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Vol. XXVII, No. 5 MAY, 1938

JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

TRADE MARK

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THE 86th ANNUAL MEETING OF THE AMERICAN PHARMACEUTICAL ASSOCIATION WILL BE HELD IN MINNEAPOLIS, MINN., Hotel Nicollet, August 22–27, 1938.

The 1938 Meetings of the American Association of Colleges of Pharmacy, the National Association of Boards of Pharmacy, Conference of Pharmaceutical Association Secretaries, of the Pharmaceutical Law Enforcement Officials and the Plant Science Seminar will also be held in Minneapolis, Minn.

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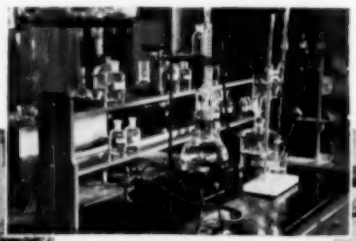

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MINNESOTA, THE "NORTH STAR STATE," AWAITS AMERICA'S DRUGGISTS.

The pharmacists of America are already planning the vacation dream of a lifetime in Minneapolis, land of Laughing Water, Minnehaha and Hiawatha. Fishing kits and bathing suits are even at this early date being pulled out from closet and den, as well as golf clubs and tennis rackets. What a summer paradise!

The AMERICAN PHARMACEUTICAL ASSOCIATION, National Association Boards of Pharmacy, American Association of Colleges of Pharmacy and allied groups will hold their annual convention in Minneapolis, where eleven beautiful lakes are right within the city itself and less than thirty minutes from the hotels in the loop. Most of these lakes are large enough for fishing, sailing and canoeing. They provide bathing beaches for hundreds of thousands of outdoor lovers each year. In Minnehaha Park the "Falls of Minnehaha" leap and play.

In the month of August Minnesota excels any vacation land in the world. Its gigantic forests, its crystal clear, pine-scented air, its lakes and meadows, invigorate body, soul and mind.

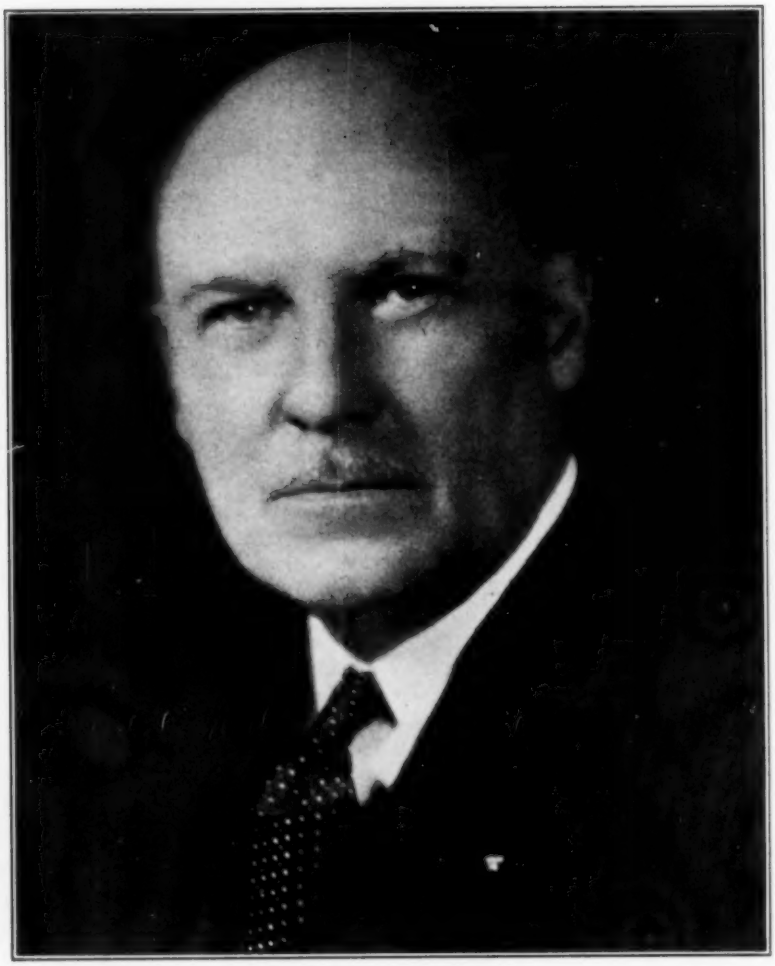
Every effort will be made by all Minnesotans to fulfil every vacation dream of the nation's watchers and defenders of the public health. The Seminars, conferences and social programs may be many, but there will be ample time to partake of unrivaled bathing, of sun-lolling on myriad beaches, of horseback riding under towering pines, of golfing and tennis, and the joy of joys—matchless fishing where handsome, husky fish make a real battle and real eating. An over night woodland cabin, a lakeside camp, a river bivouac, all but thirty minutes from the heart of either Minneapolis or St. Paul. Ever-changing vacation fun that gives life new color, new zest, new meaning.

Beside the incomparable joys of the great outdoors, the stimulus of the pharmaceutical profession's outstanding leaders will inspire and bring about an ever-broadening field in the beneficent services of pharmacological science and the prevention of damage to the public health.

Dean Charles H. Rogers of the Minnesota College of Pharmacy, and his committee, have started the ball rolling and the goal is the happiest, merriest and most forward-moving convention that the national association has ever held. Out of it will come an improved health service in which the welfare of the nation will be greatly stepped up.

On to Minnesota—August 21st to 27th. The "land of sky blue waters" accepts the challenge to outdo itself in hospitality for the great convention.

NOTE: For detailed information as to the myriad vacation pleasures of the state, address Tourist Bureau, State Capitol, St. Paul, Minn.



HENRY C. CHRISTENSEN.

JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

VOL. XXVII MAY, 1938 No. 5

HENRY C. CHRISTENSEN.

The Remington Medal is presented annually to "the man or woman who has done most for American Pharmacy during the preceding year or during a longer period of outstanding activity or of fruitful accomplishment." It is the outstanding award for general achievement in Pharmacy.

The award of this medal for 1938, to Dr. Christensen, is a well-deserved and crowning recognition of the splendid work he has done as a practicing pharmacist, as a member of the Board of Pharmacy, as Secretary of the National Association Boards of Pharmacy, as President of the AMERICAN PHARMACEUTICAL ASSOCIATION, as an officer of the National Drug Trade Conference, as the organizer and director of the Pharmacy Exhibits at the Century of Progress Exposition in Chicago and the Texas Centennial Exposition in Dallas, as a member of the American Council on Pharmaceutical Education and in many other positions of honor and responsibility. Dr. Christensen is recognized as a good citizen, as a sound thinker and effective worker, as having strong convictions and the courage to support them, as a modest, kindly gentleman and loyal friend and as a good son, husband and father.

Biographies of Dr. Christensen have appeared in this JOURNAL (April 1930) and in other publications; and it is not necessary, therefore, to again record here the details of his busy and useful life, which has been devoted largely to his profession. It is another story of what a man with ability, honesty and perseverance can do and become, in America, if he is willing to work. It is probable that in time to come Dr. Christensen's efforts as Secretary of the N. A. B. P. since 1914, in establishing and perfecting the system of interstate registration of pharmacists, which is now accepted as one of the best in the professions, in coördinating the activities of the examining boards and the teaching institutions, and in strengthening and extending pharmaceutical legislation will be looked upon as his greatest contributions to Pharmacy and to the general welfare. This work has had his major attention and has taken him into every state in the Union. He has made a host of friends and acquaintances and is recognized as a positive force for good.

The medal will be presented at a meeting of the New York Branch of this ASSOCIATION, to be announced later. The JOURNAL extends hearty congratulations to Dr. and Mrs. Christensen and other members of his family, including his mother who is still active.—E. F. K.

EDITORIAL

E. G. EBERLE, EDITOR 2215 Constitution Ave., WASHINGTON, D. C.

NATIONAL LEGISLATION.

During the closing session of the Seventy-Fifth Congress, four bills were enacted that are of direct interest to the profession of Pharmacy not only because of their provisions or exemptions but also because they will in all probability become the patterns for state legislation on these important subjects. Two of these acts were passed earlier in the session and have had presidential approval; it is expected that the others will also be approved. It is not possible to more than briefly refer to these measures at this time and they will be the subjects of extended consideration at the Minneapolis meeting.

The ASSOCIATION has kept in close touch with these bills during their legislative progress and has attempted to see that the interests of the profession had consideration. The members of the Congress who had the measures in charge invited criticisms and suggestions for their improvement.

VENEREAL DISEASE CONTROL.

The LaFollette-Bulwinkle Bill provides for the expenditure of $15,000,000 over a period of three years from July 1, 1938, "For the purpose of assisting states, counties, health districts, and other political subdivisions of the states in establishing and maintaining adequate measures for the prevention, treatment and control of venereal diseases." Of this sum $3,000,000 are to be spent during the first, $5,000,000 during the second and $7,000,000 during the third year, in accordance with plans presented by the health authority of the state and approved by the Surgeon General of the Public Health Service.

The pharmacists of this country have a great responsibility and a real opportunity in this campaign. State and local pharmaceutical associations are urged to promptly contact their state and local health authorities to learn how the pharmacists may coöperate in such an important public health movement. A considerable portion of these large sums will be expended for drugs, medicines and medical supplies, largely under the direction of the state health authorities, and pharmacists should carefully investigate the opportunities open to them.

FAIR LABOR STANDARDS ACT.

This act, S. 2475 and generally referred to as the Wages and Hours Bill, provides for the establishment of labor standards with respect to minimum wages and maximum hours in industries engaged in interstate commerce or engaged in the production of goods for such commerce. These provisions do not apply to any employee employed in a bona fide professional or local retailing capacity and pharmacists are therefore exempt in so far as these activities are concerned.

FEDERAL TRADE COMMISSION ACT, S. 1077.

This amendment to the Act establishing the Commission, had two general purposes: *First*, to broaden the powers of the Commission over unfair methods of

competition by giving it jurisdiction over unfair or deceptive acts or practices in commerce whether competitive or not; and, *second*, to give the Commission more effective control over false advertisement of foods, drugs, devices and cosmetics. The broad definitions of foods, drugs, devices and cosmetics as employed in the Federal Food, Drug and Cosmetic Act, S. 5, are employed in S. 1077 and false advertisement of any of them for the purposes of this Act "means an advertisement, other than labeling, which is misleading in a material respect; and in determining whether any advertisement is misleading, there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, sound or any combination thereof, but also the extent to which the advertisement fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the commodity to which the advertisement relates."

The Commission is given broad control of false advertisement of foods, drugs, devices and cosmetics other than labeling, which is under the control of the Food and Drug Administration under S. 5, and the administration of S. 1077 and S. 5 should remedy the abuses which have existed in the advertising of these products.

FEDERAL FOOD, DRUG AND COSMETIC ACT, S. 5.

As is well known, this legislation has been under consideration since 1933. In the form enacted, it brings medical devices and cosmetics under its provisions and requires that no new drug shall be introduced or delivered for introduction into interstate commerce unless an application has been filed with the Secretary of Agriculture giving full information to show that the drug is or is not safe for use and unless the secretary has not issued an order within the time specified, refusing to permit the application to become effective. The provisions and penalties of the present act are broadened in many other respects, and it is generally believed that the law represents a decided improvement over that now in effect. Senator Copeland said upon the passage of the bill by the Senate, "We now have a bill which may bring disappointment to some, but I think it marks a very great advance, probably beyond that of any country in the world." Representative Lea who was in charge of the bill in the House, said in commenting on the work of his committee, that "our differences of opinion have in the end worked to give us better legislation."

The definitions of foods, drugs, devices and cosmetics in this act are similar to those in the Federal Trade Commission Act and are very inclusive. The provisions with respect to the adulteration and misbranding of drugs and devices and the exemptions from the misbranding provisions which cover prescriptions should be carefully studied. The ASSOCIATION has expressed its earnest desire to have food, drug and cosmetic legislation enacted and its conviction that further delay was against the public interest, and has done what it could toward the successful outcome.

The enactment of the four measures referred to above is an important development for the public health professions and for the American people. Pharmacy should lend its support to the successful administration of these acts and to such amendments of them as experience may show to be desirable or necessary for the adequate protection of the public welfare.—E. F. K.

A SECOND U. S. P. SUPPLEMENT.

At the recent meeting of the U. S. P. Board of Trustees, authority was given for the publication of the Second U. S. P. XI Supplement. It is hoped that this can be printed and released on January 1, 1939.

Preparation for the Supplement has been under way for months and Sub-Committee chairmen will be in a position in the near future to submit reports on a number of revised texts. The Sub-Committee on Scope is also considering the admission of a number of additional important new drugs. The members of our Committee are fully familiar with the outstanding advantages of the Interim Revision and Supplement features of the Pharmacopœial program. This gives the opportunity to issue new standards after they have been subjected to extensive checking in many laboratories.

Our former decennial revision method compelled the consideration of between five and six hundred items simultaneously and then at the end of the revision period it became necessary to go to press with the entire lot, irrespective of the status of their revision. Of necessity, with some Sub-Committee chairmen handling from a hundred to a hundred and seventy-five separate monographs, it was impossible to give each article the exacting consideration and extensive review which has been possible under the new plan by which only a dozen or so monographs are under revision at one time. The Supplement is also permitting the prompt recognition by the Pharmacopœia of important new medicines and, as indicated above, this will be a feature of the Second Supplement.

The U. S. P. Board of Trustees modified the original plan for the issuance of *annual supplements* before the "First Supplement" was issued, on the ground that a more flexible plan seemed necessary. They became convinced that in some years circumstances might make it necessary to issue a new Supplement before twelve months had passed, while under other conditions an additional Supplement might not be required for several years. The Board therefore announced, through the medical and pharmaceutical press, that new U. S. P. Supplements would be issued whenever in the judgment of the Committee of Revision and Board of Trustees, conditions made this desirable.

The Pharmacopœia Board or Committee of Revision is responsible only for the preparation of the official standards. Whether or not the Pharmacopœia and its Supplements are purchased by retail pharmacists is, in some states, entirely optional. In other states where the State Law requires the possession of these books, it is a matter for the responsible state officials to enforce.

The U. S. P. finances are in excellent condition and the Board of Trustees has been able to meet the revision expenses of the decade, to greatly increase the research and conference programs, and to still hold its basic reserves intact.

In preparing the Second Supplement, every step will be taken to insure the carrying out of the requirements of the Convention for the preparation of an official text. It is expected that the revised, or new, monographs will be submitted in the form of proof to members of the Committee of Revision and given wide publicity. Following their publication, a public hearing will be granted at which members of the Executive Committee responsible for revised texts will be in attendance. Following the public hearing a conference with the officials of the

Food and Drug Administration and the Public Health Service will be held, after which the members of the Committee of Revision will be given an opportunity to see and vote upon the finally approved text. When the Second U. S. P. XI Supplement has been issued, ample time will be given before it becomes official.

INTERNATIONAL TECHNICAL COMMISSION OF PHARMACOPŒIAL EXPERTS.

At the recent session of the Health Organization of the League of Nations, a Commission was appointed to carry on the work of the Brussels' Conference for the establishment of standards for potent medicines. The Committee consists of:

Chairman, Dr. C. H. Hampshire, London; Professor H. Baggesgaard, Copenhagen; Professor V. E. Zunz, Brussels; Professor M. Tiffeneau, Paris; Professor R. Eder, Zurich; Professor L. van Itallie, Leyden; Professor E. Fullerton Cook, Philadelphia; a member of the Union of Soviet Socialist Republics.

The Brussels' Conference was the outgrowth of earlier efforts to establish an International Pharmacopœia. In 1902 a group of pharmacists from Brussels, in the name of the Belgian Government, issued invitations to practically all nations of the world to participate in a conference for the purpose of establishing uniformity in the definition and strength of the more potent medicines in use throughout the world.

At that time, the Pharmacopœia of the United States was officially represented by Dr. H. C. Wood, Sr., then one of the leading pharmacologists of the world, and by Dr. Frederick B. Power. The Chairman of the Committee of Revision, Professor Joseph P. Remington, was at that time greatly interested in this international movement and in a contribution to the conference urged the practical policy of establishing standards meeting the approval of the conference and offering these to the Pharmacopœial Commissions throughout the world for voluntary adoption.

The importance of this at the time can scarcely be appreciated. In the U. S. Pharmacopœia the Syrup of Ferrous Iodide was 10 per cent; Tincture of Capsicum, 5 per cent; Tincture of Aconite, approximately 35 per cent; Tincture of Veratrum 40 per cent, Tincture of Belladonna, 15 per cent. This conference established 10 per cent as the strength for all potent Tinctures and 20 per cent for Tinctures of non-potent drugs like Cinchona and Gentian, with 5 per cent for Syrup of Ferrous Iodide. The Eighth Revision of the U. S. Pharmacopœia, published in 1905, was the first National Pharmacopœia to adopt the standards of this International Protocol (P. I.) as recommended by the 1902 Brussels' Conference.

A Second Conference was called for 1914, but was postponed because of the World War. The Second Conference was finally assembled at Brussels in 1925, with representatives from more than forty nations participating. Additional uniformity in standards and preparations was recommended at that time and the Conference adjourned after passing recommendations that its work be taken over by the Health Organization of the League of Nations.

The establishment of a Pharmacopœial Secretaryship, at the League, has been the basis for discussion for many years but the actual establishment of the program has only now been completed. The chairman of the Committee, Dr. Hamp-

shire, is the secretary of the British Pharmacopœial Commission, which has recently published the First Supplement to the British Pharmacopœia.

This International Commission plans to compile a list of the more important medicines used throughout the world and invite the respective National Pharmacopœial Commissions in various countries to prepare model monographs, which when finally approved will be presented to the Pharmacopœial Commissions of the world with the hope that they may assist in bringing about greater uniformity in titles, definitions, descriptions, tests for identity and purity and methods of assay.

It is hoped that the International Commission may also be able to compile the Pharmacopœial literature of the world for the use of all Pharmacopœial Commissions, thus avoiding the duplication of literature reviews by each nation. It will, of course, be necessary in each nation to appoint associate members from their Pharmacopœial Committees to assist in the actual preparation of monographs.

MEETING OF TECHNICAL COMMISSION OF PHARMACOPŒIAL EXPERTS, HEALTH ORGANIZATION, LEAGUE OF NATIONS.*

The Technical Commission of Pharmacopœial Experts, appointed by the Council of the League of Nations at its meeting in January last, met at Geneva in May 1938.

The Commission's task was to prepare a program of studies, select suitable drugs for examination and determine a uniform method of analysis, assay and preparation of the drugs selected.

The necessity for such work arises from the difficulties encountered by pharmacists in dispensing prescriptions for travelers from foreign countries and in the replenishment of medicine chests of ships at ports of call. Unification would, in addition, be of great advantage to manufacturers and would facilitate commerce in drugs between nations. Further, it would assist in the comparability of the results of medical treatment in different countries.

The Commission prepared a list of the more important drugs which it proposed to study and codify. Draft schemes for the preparation of monographs on the drugs were agreed upon, and a number of general principles were settled.

The list of drugs was divided among the members of the Commission for the purpose of study in collaboration with experts in their own countries.

ANNUAL MEETING OF THE BOARD OF TRUSTEES, UNITED STATES PHARMACOPŒIAL CONVENTION.

The Annual Meeting held at Pittsburgh, Pa., May 16th and 17th developed many facts of interest and importance to the Medical and Pharmaceutical professions. Reports submitted by the officers, the chairman of the Revision Committee and the auditor showed marked progress and a satisfactory financial situation.

Of the original issue of 50,000 copies of U. S. P. XI, more than 45,000 have been distributed and a second printing is now under way. Approximately 6000 copies of the first Supplement have been sold to date and the Board authorized the chair-

* Since the above article was written the following report has been received.

man of the Revision Committee to proceed with the preparation of a second Supplement to be made available about Jan. 1, 1939. The Spanish Edition of U. S. P. XI was most favorably received and has gained wide recognition throughout Central and South America.

Experiments now being conducted to determine the potency of Vitamin A by the Spectrophotographic method are progressing satisfactorily. This method may be introduced into the U. S. P. Cod Liver Oil text as a partial indication of value. With carefully selected material supplied by the Board, a group of heart specialists in this and other countries will conduct certain studies on clinical activity and deterioration of Digitalis which will be paralleled by biological assays by various methods. The entire investigation will cover a period of three years. The influence of the Anti-Anemia Board in clarifying the liver preparations situation is deemed well nigh incalculable and the work of this Board is progressing most satisfactorily.

The meeting of the Board of Trustees closed with the reëlection of the following officers: James H. Beal, *Chairman;* Samuel C. Henry, *Secretary.*

ASSEMBLY OF LABORATORY DIRECTORS AND SEROLOGISTS.

In Hot Springs National Park, Arkansas, October 21–22, 1938, will be held a convention of Serologists and Directors of Laboratories, under the auspices of the Committee on Evaluation of Serodiagnostic Tests for Syphilis, with Surgeon General Thomas Parran as chairman.

The aims and purposes of the assembly will be to consider means and methods to improve and to make more generally available the serologic tests, which are so important in syphilis control work. Tentative arrangements call for the presentation of the program in four sections.

The first section will consider the need for adherence to conventional technique in the routine performance of reliable serodiagnostic tests. This subject will be considered in papers by Doctors Harry Eagle, William A. Hinton, Reuben Kahn, Benjamin Kline and John H. Kolmer, with special reference to the tests which each of these workers has described.

Need for training of laboratory personnel will be the subject of the second section. The qualifications and training for both laboratory directors and technicians will be presented in separate papers.

The third section will discuss the prosecution of the studies to evaluate the performance of serologic tests within the states. The efficiency of branch state laboratories and of municipal, hospital and private laboratories cannot be studied on a national basis. The subject is much too large. Should this be made a function of the state or large municipal department of health? Actual experience with such studies in the states of Maryland and New Jersey and in the city of Cleveland will be described.

The fourth section will consider the desirability of licensing or approving for the performance of serodiagnositc tests for syphilis, laboratories within the states by the respective state departments of health. This discussion will be conducted from the standpoint of the private laboratory director by Doctor Frederick H. Lamb of Davenport, Iowa. The health officer's side will be presented by Doctor A. Wadsworth, State Department of Health, Albany, New York.

A separate committee will draft recommendations for each of the four sections for presentation to the assembly. The respective chairmen of these four section meetings will be Doctors Walter M. Simpson, Dayton, Ohio; Arthur H. Sanford, Rochester, Minnesota; F. E. Senear, Chicago, Illinois; and H. H. Hazen, Washington, D. C. General discussion will follow the presentation of each set of recommendations.

An additional feature of the meeting will be an actual demonstration of the performance of the Eagle, Hinton, Kahn, Kline and Kolmer tests by the originators of these procedures.

It is to be hoped that the attendance at this assembly will be large. Out of the meeting should come a crystallization of opinion with regard to the important problems which will be considered. Those interested in obtaining further information should write to the Surgeon General, U. S. Public Health Service, Washington, D. C.

SCIENTIFIC SECTION

BOARD OF REVIEW OF PAPERS.—*Chairman*, F. E. Bibbins; H. M. Burlage, W. G. Crockett, E. V. Lynn, C. O. Lee, L. W. Rising, L. W. Rowe, Heber W. Youngken, Ralph E. Terry, Carl J. Klemme.

DETERMINATION OF THE REASONABLE OR PERMISSIBLE MARGIN OF ERROR IN DISPENSING. VI. ELASTIC FILLED CAPSULES.*[1]

BY MARVIN J. ANDREWS.[2]

In the first five papers of this series, a study was made of the different types of prescriptions which the pharmacist usually compounds in his own laboratory. The five papers presented to date deal with (1) powders and capsules, (2) ointments, (3) suppositories, (4) pills and (5) liquids. This, the sixth paper, deals with elastic filled capsules.

Prescriptions calling for liquids or suspensions in capsules usually fall within one of three classes, that is, (1) liquids in hard gelatin capsules, (2) liquids to be placed in empty soluble elastic capsules, and (3) soluble elastic filled capsules prepared by manufacturing concerns. As the first two classes are seldom prescribed, the study in this paper is limited to the variation in weight of soluble elastic filled capsules prepared by different manufacturing concerns and dispensed by the retail pharmacist.

Elastic filled gelatin capsules are usually prepared commercially by one of the following methods: (1) the plate mold and press method or (2) rotary die process. Briefly, the first method consists of placing a warmed sheet or leaf of gelatin over the bottom mold, adding the correct weight or volume of medicament, covering this with a second sheet of gelatin followed by the top plate of the mold. The set of molds is then placed under a press and pressure applied. When the pressure on the press is released, and the top plate of the mold removed, the finished capsules are removed by stretching the net. The second, or the rotary die machine (see Remington's Practice of Pharmacy, 8th Edition, page 1687) is a self-contained unit which produces filled capsules continuously and automatically. Two continuous gelatin ribbons are brought between a pair of revolving dies and an injection wedge which adds the medicament, and as the die revolves, it seals and severs the filled capsule.

EXPERIMENTAL PART.

For the purpose of this study the different types of elastic filled capsules which the pharmacist is most frequently called upon to dispense, were divided into two general classes, namely: (1) liquids in transparent capsules and (2) suspensions in non-transparent capsules.

To discover if there was any appreciable variation in the weight of individual elastic machine filled gelatin capsules, three series of tests were carried out. The first series of tests was conducted to determine the variation in weight, if any, of transparent capsules prepared in the same capacity molds and filled with different liquids by the same manufacturer. The second series was limited to liquids in transparent capsules containing fish liver oils, made by the same and different manufacturers. The principal object of the third series was to determine the variation in weight of suspensions in non-transparent capsules. The capsules in each instance were weighed directly, capsule with contents, as it was impossible to completely remove the contents from the capsules.

* Section on Practical Pharmacy & Dispensing, A. PH. A., New York meeting, 1937.

[1] From the Department of Pharmacy, School of Pharmacy, University of Maryland.

[2] Assistant Professor of Pharmacy, School of Pharmacy, University of Maryland.

A definite letter was assigned to each manufacturer whose products were used in these series of tests.

SERIES I.

In the first series of tests 10 capsules were selected at random from boxes of the same lot, made by manufacturer A. The samples selected bore the following labels: (1) santal oil, 5m̃, (2) benzyl benzoate, 5m̃, (3) creosote carbonate, 5m̃, (4 and 5) a speciality product and (6) castor oil, 20m̃.

The results of the first series of tests are presented in Table I on page 376.

The tabulated data given in Table I shows there is a variation in weight of individual filled liquid capsules taken from the same batch made by the same manufacturer. Likewise, there is a variation in the different varieties of capsules made in the same mold as indicated by comparison. In number one to three, 5 minim mold, the standard deviation is lowest for No. 2, S. D. equals 0.019 Gm. corresponding to 3.93%, while the highest is No. 3 with a S. D. of 0.036 Gm. corresponding to 7.05%.

As the size of the capsule increases (No. 6) the S. D. increases with a decrease in the percentage deviation. Numbers 4 and 5 indicate there is also a variation in the weight of two different lots of the same proprietary product.

SERIES II.

In the second series of tests a selection was made of frequently used 3 minimum transparent elastic capsules containing fish liver oils made by the same and different manufacturers. Each sample of ten represents capsules of a definite lot. The contents and manufacturer of each sample are as follows: Numbers 7 and 8—Haliver Oil with Viosterol made by manufacturer B; numbers 9, 10, 11 and 12—Haliver Oil with Viosterol made by manufacturer C; numbers 13 and 14—fish liver oil made by manufacturer D and sold under a trade name, and lastly numbers 15 and 16 which contain standardized cod liver oil made and sold under a trade name by manufacturer E.

The results of the second series of tests are presented in Table II on page 376

The greatest variation in the Haliver Oil with Viosterol elastic filled capsules was noted in sample number 10 with a standard deviation of 0.029 Gm. corresponding to 8.92%, while the smallest variation was number 7 with a standard deviation of 0.015 Gm. corresponding to 3.49%. The capsules containing fish liver oils and sold under a trade name, although slightly smaller, with the exception of number 13, proved to be more uniform than any of the others in this series. The minimum variation for the entire series was sample number 15 with a standard deviation of 0.004 Gm. corresponding to 1.37% while the highest variation was found to be sample number 10 with a standard deviation of 0.029 Gm. corresponding to 8.92%.

SERIES III.

The third series of tests was performed to determine the variation in weight, if any, of non-transparent capsules filled with a suspension in oil. For this series the popular brands of capsules containing combinations of vitamins A, B, D and G were selected.

The consistency of the contents of these samples varied from a relatively limpid liquid containing a suspension to a thin paste. To date we have not had sufficient replies from the manufacturers to make a definite statement as to what type machine these products were made in, neither do we know whether the medicaments were weighed or measured, with two exceptions—manufacturer A capsules are made on the plate mold and press machine, the medicament being measured, while those of manufacturer F were made on the Rotary Die machine. However, from general information, one would expect the variation to be slightly higher than in the case of transparent capsules filled with a clear liquid. The manufacturers of the products used are as follows: numbers 17, 18, 19 and 20, manufacturer B; numbers 21, 22 and 23, manufacturer C; number 24, manufacturer D; and numbers 25 and 26, manufacturer F.

The results of the third series of tests are presented in Table III on page 377.

The standard deviation for the individual lots of capsules made by the same manufacturer in the third series of tests is slightly higher than those in the second series. Different lots made by the same manufacturer are quite uniform, yet there is quite a variation between different manufacturers. The lowest variation in weight is found in number 25 with a standard deviation of

TABLE I.—VARIATION IN WEIGHT OF ELASTIC FILLED CAPSULES PREPARED BY MANUFACTURER A.

Batch No.	Weight of Each Capsule in Gm. 1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	Av. Wt. in Gm.	S. D. in Gm.	% D.*	Number Falling within 1 × S. D.	2 × S. D.
1	0.515	0.451	0.443	0.473	0.484	0.485	0.432	0.495	0.501	0.523	0.480	0.028	5.83	6	4
2	0.485	0.475	0.508	0.484	0.465	0.499	0.501	0.505	0.472	0.445	0.483	0.019	3.93	7	3
3	0.454	0.495	0.497	0.531	0.529	0.530	0.445	0.531	0.519	0.571	0.510	0.036	7.05	7	3
4	0.971	1.081	1.042	1.102	0.932	0.986	0.926	1.041	1.018	1.061	1.016	0.057	5.61	6	4
5	1.036	1.174	1.015	0.994	1.017	1.177	1.095	1.011	1.022	0.925	1.046	0.075	7.17	6	4
6	1.956	1.962	1.891	1.912	1.958	1.746	1.873	1.832	1.787	2.013	1.893	0.066	3.49	6	4

* Percentage deviation based on average weight.

TABLE II.—VARIATION IN WEIGHT OF 3 MINIMUM ELASTIC FILLED CAPSULES PREPARED BY THE SAME AND DIFFERENT MANUFACTURERS.

Batch No.	Mfg.	Weight of Each Capsule in Gm. 1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	Av. Wt. in Gm.	S. D. in Gm.	% D.*	Number Falling within 1 × S. D.	2 × S. D.	3 × S. D.
7	B	0.421	0.415	0.432	0.450	0.423	0.453	0.432	0.419	0.405	0.446	0.429	0.015	3.49	6	4	..
8	B	0.536	0.545	0.516	0.466	0.463	0.485	0.511	0.509	0.497	0.543	0.507	0.028	5.52	5	5	..
9	C	0.269	0.276	0.306	0.279	0.270	0.279	0.302	0.291	0.284	0.236	0.279	0.019	6.81	7	2	1
10	C	0.333	0.307	0.334	0.382	0.295	0.330	0.333	0.315	0.271	0.346	0.325	0.029	8.92	6	4	..
11	C	0.291	0.293	0.263	0.296	0.243	0.300	0.315	0.301	0.293	0.282	0.288	0.020	6.94	7	2	1
12	C	0.321	0.283	0.353	0.367	0.335	0.296	0.340	0.331	0.339	0.347	0.331	0.024	7.25	7	3	..
13	D	0.261	0.263	0.254	0.272	0.255	0.243	0.263	0.232	0.240	0.234	0.252	0.013	5.15	7	3	..
14	D	0.262	0.276	0.282	0.262	0.271	0.265	0.267	0.262	0.275	0.267	0.269	0.007	2.60	9	1	..
15	E	0.291	0.293	0.281	0.286	0.291	0.292	0.293	0.292	0.292	0.295	0.291	0.004	1.37	8	1	1
16	E	0.305	0.307	0.307	0.290	0.286	0.284	0.290	0.284	0.285	0.287	0.293	0.009	3.07	7	3	..

* Percentage deviation based on average weight.

TABLE III.—VARIATION IN WEIGHT OF NON-TRANSPARENT CAPSULES FILLED WITH A SUSPENSION IN OIL.

Batch No.	Mfg.	Weight of Each Capsule in Gm. 1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	Av. Wt. in Gm.	S. D. in Gm.	% D.*	Number Falling within 1 × S. D.	2 × S. D.	3 × S. D.
17	B	0.465	0.474	0.510	0.524	0.543	0.541	0.571	0.540	0.602	0.525	0.530	0.039	7.36	6	4	..
18	B	0.563	0.549	0.479	0.502	0.610	0.553	0.511	0.547	0.515	0.486	0.532	0.038	7.14	7	2	1
19	B	0.505	0.543	0.551	0.548	0.553	0.497	0.546	0.590	0.527	0.522	0.538	0.025	4.64	8	1	1
20	B	0.537	0.522	0.546	0.533	0.580	0.547	0.526	p.571	0.518	0.533	0.541	0.019	3.51	7	2	1
21	C	0.523	0.593	0.437	0.513	0.591	0.503	0.490	0.491	0.468	0.446	0.505	0.051	10.09	7	3	..
22	C	0.506	0.538	0.559	0.611	0.446	0.568	0.664	0.578	0.524	0.480	0.547	0.060	10.96	6	4	..
23	C	0.584	0.597	0.500	0.606	0.561	0.564	0.491	0.601	0.591	0.520	0.562	0.041	7.29	6	4	..
24	D	0.631	0.645	0.599	0.637	0.641	0.643	0.621	0.640	0.622	0.633	0.631	0.013	2.06	8	1	1
25	F	0.512	0.511	0.506	0.501	0.497	0.524	0.513	0.503	0.508	0.499	0.507	0.008	1.58	8	1	1
26	F	0.519	0.526	0.531	0.516	0.514	0.547	0.534	0.537	0.517	0.531	0.527	0.010	1.90	7	3	..

* Percentage deviation based on average weight.

0.008 Gm. corresponding to 1.58%, while the highest is number 22 with a standard deviation of 0.060 Gm. corresponding to 10.96%. This wide variation in products made by different manufacturers is no doubt due to the thickness and uniformity of the coating; the consistency of the suspension in oil; the accuracy with which this suspension is measured or weighed; the uniformity with which it is distributed in preparing the capsules; and the type machine used in making the products.

For the purpose of making it possible to more readily compare the results of these three series with similar data that have been published, but which have not been expressed in terms of the standard deviation, the per cent of deviation from the average weight has been calculated and is presented in Table IV.

TABLE IV.—PERCENTAGE OF ERROR COMPUTED FROM DATA IN TABLES I, II AND III.

Batch Number.	Mfg.	Average Weight in Gm.	Number of Capsules Falling within 1%.	2%.	3%.	4%.	5%.	6%.	7%.	8%.	9%.	10%.	11%.	12%.	13% or Over.
1	A	0.480	2	1	..	1	1	1	..	2	1	1	..	..	..
2	A	0.483	2	1	1	3	1	1	..	1	..	..	..	..	..
3	A	0.510	..	1	2	2	2	..	..	..	..	..	1	1	1
4	A	1.016	1	..	3	..	2	..	1	..	3	..	..	..	..
5	A	1.046	1	..	3	1	2	..	..	..	..	..	..	1	2
6	A	1.893	3	1	..	4	..	2	..	1	..	..	..	..	..
7	B	0.429	2	2	1	2	1	2	..	..	..	..	..	..	..
8	B	0.507	2	2	..	..	1	1	..	3	2	..	..	..	..
9	C	0.279	3	1	1	2	..	..	..	1	1	..	..	..	1
10	C	0.325	..	1	3	1	..	1	1	..	..	1	..	..	2
11	C	0.288	1	2	2	1	1	..	..	..	2	..	..	..	1
12	C	0.331	1	1	2	1	..	1	..	1	..	..	..	2	1
13	D	0.252	2	..	..	2	3	..	1	1	1	..	..	..	..
14	D	0.269	3	2	4	..	1	..	..	..	..	..	..	..	..
15	E	0.291	2	6	1	1	..	..	..	..	..	..	..	..	..
16	E	0.293	2	1	4	1	2	..	..	..	..	..	..	..	..
17	B	0.530	1	2	2	1	..	..	..	1	..	..	..	1	2
18	B	0.532	..	..	1	2	2	1	1	..	..	1	1	..	1
19	B	0.538	1	2	3	1	..	..	1	..	1	..	1	..	..
20	B	0.541	2	3	1	1	1	1	..	1	..	..	..	..	..
21	C	0.505	1	1	2	1	..	..	..	1	..	..	..	1	3
22	C	0.547	..	1	1	..	2	..	1	..	1	..	..	..	4
23	C	0.562	2	..	..	1	1	1	2	1	..	..	1	1	..
24	D	0.631	4	4	1	..	1	..	..	..	..	..	..	..	..
25	F	0.507	5	4	..	1	..	..	..	..	..	..	..	..	..
26	F	0.527	3	4	2	1	..	..	..	..	..	..	..	..	..

NOTE: All percentages are calculated from the average weight. 1% equals 1% or less; 2% equals from 1% plus to 2%; etc.

The results of Tables I, II and III are summarized in Table V which follows.

TABLE V.

Series No.	Number of Capsules Falling within 1 × S. D.	2 × S. D.	3 × S. D.
I	38	22	
II	69	28	3
III	70	25	5
Totals	177	75	8

An examination of the tables shows that 93.92% (68.08% and 28.84%) of a total of the 260 capsules weighed fall within twice the standard de[illegible] as the capsules used in these tests are concerned, therefore, the deviation might well be [illegible] defining the limit for reasonable or permissible error.

CONCLUSIONS.

1. The factors largely responsible for the variation in weight of machine made elastic filled gelatin capsules are (1) the uniformity in thickness and elasticity of the gelatin sheet used as the shell, (2) the accuracy with which the medicament is measured or weighed, (3) the uniformity of the molds, (4) the uniformity with which the medicament is distributed throughout the capsules of one batch, and (5) the uniformity of pressure applied by the machine in sealing.

2. From the data obtained in the tests made it would seem that twice the standard deviation is a reasonable margin of error for machine made elastic filled gelatin capsules. This would include 96.92% of the capsules weighed.

REFERENCES.

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(2) Andrews, Marvin J., *Ibid.*, 23, 350 and 421 (1934).
(3) Andrews, Marvin J., *Ibid.*, 23, 1003 (1934).
(4) Andrews, Marvin J., *Ibid.*, 23, 1117 and 1210 (1934).
(5) Andrews, Marvin J., *Ibid.*, 24, 477 (1935).

A STUDY OF ENTERIC COATINGS.[1]

BY J. T. GOORLEY[2] AND C. O. LEE.[3]

INTRODUCTION.

For many years pharmacists have tried to prepare medicines so that they would not be liberated for absorption until they had reached the intestine. Therefore, studies have been made from time to time to determine the value of enteric coatings by various test-tube methods. More recently attempts have been made to trace the disintegration of enteric coatings in the body by means of the X-ray.

The purposes of this investigation were: *First*, to study the physiological processes to which enteric coatings are subjected; *second*, to study the relative merits of the materials now used for enteric coatings; and *third*, to provide a more reliable enteric coating. The study of the passage of coated pills and capsules through the body was made possible by the installation of a General Electric X-ray machine in the Purdue University School of Pharmacy.

It was pointed out as early as 1889 by Bourquelot (1) that there are at least four classes of medicines which should be enterically coated. They are as follows:

(1) Medicines that by prolonged contact cause irritation to the stomach.
(2) Medicine that can injure the digestion by giving insoluble precipitates with pepsin and peptones.
(3) Medicines that are rendered inactive or decomposed by the gastric juice.
(4) Medicines which should arrive in the intestine as concentrated as possible.

In addition to the types of medicines mentioned above, the logic of enteric medication is evidenced by the fact that the intestine is the normal site for absorption. Former investigators have not taken the physiological factors influencing

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disintegration of the coatings into consideration. The importance of enteric medication to the pharmaceutical profession is borne out in a report by Jordan (2) who stated that 3.3 per cent of all prescriptions were orders for enterically coated medicines.

There are no standards in common use for the testing of enteric coatings. The tests which we made *in vitro* were similar to those outlined by Martindale and Westcott (3) and Wruble (4). The resistance to four hours of acid-pepsin solution was used as a basis for estimating the value of our coatings *in vitro*. This, however, is but a reasonable arbitrary limit, being at best no more than an approximation of the average emptying time of the stomach.

For our tests "*in vivo*" extensive use was made of the fluoroscope and the X-ray. The procedures and techniques will be described later in this paper.

THE PHYSIOLOGICAL FACTORS INFLUENCING THE DISINTEGRATION OF ENTERIC COATINGS.

An understanding of the physiological and chemical reactions of the alimentary tract is necessary before the administration of enteric coatings can be intelligently considered. There are many physiological factors which affect the passage of pills and capsules from the stomach and influence their subsequent disintegration. The most important of these are:

(1) The time required for the pills or capsules to pass from the stomach.

Murlin (5) reported the stomach emptying time to be decidedly an individual matter but that the stomach should empty itself within four hours. We found that the stomach emptying time could not be depended upon as a reliable indication of the time required for the capsules to pass from the stomach. Our fluoroscopic observations revealed that in many cases capsules remained at the pyloric sphincter for a longer time than was required for the food to pass from the stomach. We attributed this to the fact that the passage of the intact capsules was hindered by the smallness of the pyloric opening, while the softened food particles were forced through the opening. We found that capsules when given about one and a half to two hours before a meal, at which time the stomach generally is empty, passed out of the stomach within a more uniform time and also that the stomach passed small capsules more uniformly than large capsules. This is an important observation since in many cases the enteric medicaments are directed to be taken at meal time and in large capsules.

(2) The acidity of the stomach and intestines.

It is well known that the stomach secretions are quite acid, ranging from about 0.2 to 0.4 per cent hydrochloric acid. The reaction of the intestinal tract is of great importance to the solution of this problem of enteric coatings, yet few of the investigators have studied the acid-alkaline condition of the intestine. The theory of enteric medication has depended too much upon the assumption that the intestine is always alkaline. A review of some of the reports on intestinal alkalinity show that this belief has been greatly over estimated. Myers and McClendon (6), McClendon and others (7), Long and Fenger (8) and Okada and Arai (9) all report the intestinal p_H range to be from 3.6 to 7.9. It was their general belief that the extreme range on the acid side was greater than that on the alkaline side.

(3) The enzyme activity of the digestive tract.

The pancreatic juice contains enzymes which are both specific and powerful in their action. These enzymes are normally present and can be depended upon to distintegrate an enteric coating composed of the substrate of one or more of these enzymes in an alkaline or acid medium. Of the three main classes of foods, fats, proteins, and carbohydrates, only fats reach the intestine unaffected by the saliva or gastric juice. From a physiological viewpoint fats should make an ideal enteric coating but when used alone they are not hard enough to withstand body temperature and peristaltic pressure.

MATERIALS STUDIED FOR THEIR ENTERIC PROPERTIES.

Keratin was the first substance proposed as an enteric coating (10). Unna reported using it in 1884 at a meeting of the Berlin Medical Society. It was used because it belongs to a class of proteins which are insoluble in acid-pepsin solution and soluble in alkali solutions. It is interesting to note that keratin was first used as a pill mass and later used as a coating. Mylius (11), Puckner (12) and several others have pointed out the failure of keratin-coated medicines to withstand acid-pepsin digestion for more than a very short time. We studied the digestibility of a sample of commercial keratin in an acid-pepsin solution using the method of Puckner and found it to be 69 per cent soluble.

SALOL.

The method of applying salol as a pill coating is described in the National Formulary III, IV and V. There are several objections to the use of salol which render it unsuitable for enteric coatings. They are: (1) Salol upon hydrolysis yields phenol (36 per cent) and salicylic acid (64 per cent) which upon prolonged use may be objectionable, for regardless of the amount taken, its physiological action cannot be ignored; (2) The minimum amount of salol required to coat pills by the National Formulary V method is about 25 per cent of the weight of the coated pill; (3) Salol is not suited for the coating of hard gelatin capsules or tablets not of a spherical shape.

The solubility of salol in buffer solutions corresponding to the p_H range of the intestine was undertaken. The procedure was as follows: To a tube containing 50 cc. of the buffer solution 0.080 Gm. of salol was added, placed in a water-bath maintained at 38° C. and stirred continuously for three hours. The contents of the tube were then filtered. The salol which remained upon the filter, the sides of the tube, and the stirrer was dissolved in chloroform. The chloroform was evaporated and the residue heated with ten cc. of 2.5% solution of sodium hydroxide on a steam-bath for five minutes. This solution was transferred to a 500-cc. iodine flask, and diluted with about 200 cc. of water. Fifty cubic centimeters of a 0.1*N* bromide-bromate solution were added together with 10 cc. of concentrated hydrochloric acid and the flask was shaken for one minute. Shaking was continued at intervals for thirty minutes, at the end of which time 10 cc. of a 15% solution of potassium iodide were added and shaking continued at intervals for 15 minutes. The free iodine was titrated with 0.1*N* thiosulfate, one cc. of 0.1*N* $Br.BrO_3$ being equivalent to 1.784 mg. of salol. The results of our analyses are shown in Table I.

TABTE I.—HYDROLYSIS OF SALOL WITH BUFFER MIXTURES.

p_H.	Cc. of Buffer.	Cc. *N*/10 $Br.BrO_3$.	Cc. *N*/10 $Na_2S_2O_3$.	Gm. Salol.	Gm. Undissolved Salol.	Per Cent Hydrolyzed Salol.
7.0	50	54.84	11.64	0.080	0.07282	8.90
7.4	50	53.12	9.05	0.080	0.07618	4.80
7.8	50	53.69	11.23	0.080	0.07604	4.90
8.0	50	52.87	14.70	0.080	0.06843	14.40
8.4	50	53.81	11.32	0.080	0.078016	2.40
Distilled Water	50	53.66	11.14	0.080	0.07586	5.10

Each of the above determinations is an average of four trials. The buffer mixtures for p_H 7.0 and 7.4 were Na_2HPO_4 and NaH_2PO_4, respectively. Those for p_H 7.8, 8.0 and 8.4 were H_3BO_3, KCl and NaOH.

Salol has been used as an enteric coating for sometime. However, it is not very reliable inasmuch as pills coated with it have been known to pass through the body intact. On the other hand, many salol coatings have been known to break in the stomach due, perhaps, to the fact that the temperature of the body is but a few degrees below that of the melting point of salol.

We have shown that salol is not hydrolyzed to any great extent in buffer solutions having ranges of p_H comparable to those of the intestine. Our observations are about the same as those reported by other workers.

A limited number of pills, which had been carefully coated with salol, were given to several subjects and their density determined by means of the X-ray. The story is as follows: 10% of them disintegrated in the intestine, 20% in the stomach, 30% failed to disintegrate and the site of disintegration of the remaining 40% was uncertain.

STEARIC ACID MIXTURES.

Stearic acid and stearic acid mixtures have long been used or suggested for use as enteric coatings. Many experiments were undertaken using combinations of stearic acid with salol, paraffin, wax, ceresin, glycosterin, lauric acid, palmitic acid, myristic acid, and stearic acid alone. The results of these experiments indicated that such substances possess the disadvantage of not forming a hard, tough coating and, because of their low melting point, cannot withstand peristaltic pressure. It might be well to note here that coatings which could be made hard with wax were so brittle that they invariably cracked on handling. Coatings containing sufficient paraffin to withstand body temperature formed a mixture which was not acted upon by the digestive juices.

SANDARAC.

Sandarac has at various times been suggested as a coating. It is interesting to note that the earlier workers used it to mask the taste of bitter pills and not for an enteric purpose. The advantage of sandarac over most resins is its ease of application. It is not nearly as sticky as shellac and can be sprayed upon the pills very conveniently. Sandarac was unsuited for our use because it does not withstand stomach acid-pepsin or stomach digestion. Observations showed that invariably some pin-point sized holes existed in the coating and that the resin did not form a varnish-like film but rather a granular surface.

SHELLAC.

Shellac has been used as a coating by the British Pharmaceutical Codex, Lascoff (13), Hilton (14) and Wruble (4). There are several disadvantages to its use. One is that it is inconvenient to apply as a coating because of its stickiness or tackiness and another is the uncertainty as to whether it is acted upon by the enzymes of the intestine.

Shellac has some properties which make it well suited for enteric purposes. It is insoluble in acid or neutral aqueous solutions and soluble in alkali solutions and alcohol. In an alcoholic solution it can be sprayed on the pills or capsules in a coating drum and the solvent quickly evaporated by means of a current of air, leaving a thin, smooth, tough film of coating on the capsules.

Tschirch (15) has shown that shellac is composed chiefly of oxygenated aliphatic acids.

MISCELLANEOUS SUBSTANCES TESTED FOR ENTERIC PROPERTIES.

The following substances were mentioned in the literature as being suitable for use as enteric coatings. The results of our studies upon them may be briefly stated as follows:

1. Collodion formed a tough film which proved to be insoluble in both stomach and intestinal fluids.
2. Tolu and benzoin. These substances failed to dry properly and showed poor enteric properties.
3. Lacquers. The samples tested were insoluble in acid and alkaline solutions.
4. Albuminoids were digested in an acid-pepsin solution.
5. Waxes. When waxes were used alone and in combination with fats, a heavy coating was formed which fissured badly upon standing.
6. Formaldehyde-gelatin. Capsules treated with formaldehyde become insoluble upon aging and are, therefore, unreliable for enteric uses.

SHELLAC AND CASTOR OIL COATINGS.

Since it was found that the intestine is not always alkaline, that a successful enteric coating must depend upon some factor other than alkalinity, and that fats are not digested until they reach the intestine, we attempted to find a coating that would possess the proper physical properties and yet be disintegrated in the intestine. Morel and Terroine (16) showed that the rate of digestibility of a series of triglycerides was influenced by the amount of unsaturated fatty acids in them. Of the fats and oils, castor oil was well suited for our purpose, containing as its chief glyceride the unsaturated ricinoleic acid. It is soluble in alcohol and mixes well with an alcoholic solution of shellac which upon evaporation leaves a thin, tough film. We found that a mixture of 20 parts of castor oil and 100 parts (by weight) of shellac in dissolved alcohol to be a satisfactory enteric mixture. In mixtures with the proportion of oil greater than this the coating was soft and would not withstand handling. The greater part of X-ray work was done upon capsules coated with this formula.

X-RAY AND FLUOROSCOPIC EXAMINATIONS.

Because we had no previous methods to follow we had to find the most suitable physiological conditions for enteric medication. At first the capsules were taken immediately after the noon meal and the individuals examined during the remainder of the day. Results from this procedure were very inconsistent even after we had developed the coating where it would hold up six hours or more in the stomach. It was commonly observed that the stomach would be empty, or nearly so, and the capsule still unbroken in the stomach.

GIVING ENTERIC CAPSULES BEFORE MEALS.

Having formulated a coating with good enteric properties, it was assumed that there should be a most favorable time for giving such medication for maximum results. An attempt was made to study the passage of capsules from the stomach when given one hour and a half to two hours before meal time.

In many cases it was observed that capsules left the stomach within 30 minutes, and in a high percentage of the cases before the next ingestion of food. Once in a while capsules would remain in the stomach from one meal to the next. However, our results indicated that enterically coated medicaments should be given one to two hours before meals. This claim is well borne out in Table II which shows what happened to 168 capsules taken by 85 subjects. Each was observed by means of the fluoroscope frequently enough to determine the path of the capsules.

These studies were made upon local townspeople who were unable, in some cases, to remain in the X-ray laboratory for the length of time necessary to complete the study. 137 of the capsules are accounted for in Table II. The remaining 31 were not successfully followed. We feel that complete observations were made upon 93 of these capsules.

The 44 capsules which are reported as "not disintegrated" are incomplete observations for reasons just stated above. However, it does show that the coatings were resistant to the gastric secretions. The capsules under this heading, as observed in the stomach, were made upon individual subjects. Furthermore, those capsules which failed to leave the stomach within three hours after ingestion are considered as unsuccessful in these observations. We feel that 89 capsules in this study proved to be reliable as far as the factors of time and disintegration are concerned.

TABLE II.—CAPSULES TAKEN BETWEEN MEALS.

Number of subjects—85
Number of capsules given—168
Number of capsules traced—137
Coating: Castor oil, shellac and alcohol mixture.

Location.	Time after Ingestion.	Capsules Disintegrated.	Capsules Not Disintegrated.
A. In Stomach	1 hour after taking	..	2
	1 1/2 hours after taking	..	2
	1 1/2 " " "	..	3
	2 " " "	..	2
	3 " " "	..	3
	3 1/2 " " "	..	*5
	4 " " "	..	2
	4 1/2 " " "	..	4
	5 1/2 " " "	..	2
	6 1/2 " " "	4	1
B. In Intestine	1/2 hour " "	..	16
	1 " " "	89	..
	1 1/2 hours " "	..	2
	Total	93	44

Observations: In three cases during the fluoroscopic observations necessary for the data in Table II capsules were observed at the moment they passed the pyloric sphincter into the duodenum. They were observed to move in a series of jerks, across the body and the length of the duodenum in about twenty seconds. This caused us to wonder whether intestinal digestion takes place in the jejunum and ileum rather than in the duodenum.

Another observation was that sodium tetraiodophenolphthalein is superior to that of barium sulfate as an opaque for this work. It dissolved readily as soon as the enteric coating broke, whereas barium sulfate, being insoluble, seemed to remain intact for some time in the broken capsule.

Tests were made upon two coatings, one much thicker and the other thinner than the one reported in Table II. The results were unsatisfactory. The thin coats broke down in the stomach and the heavier ones failed to disintegrate.

CONCLUSIONS.

1. Of the coating materials studied only shellac and shellac-castor oil mixture gave evidence of disintegrating in the intestine within a reasonable time and of not being damaged by stomach conditions.

2. The best results were obtained when the capsules were taken on an empty stomach about one to two hours before meals.

3. An enteric coating, to be successful, must be dependent upon some factor other than alkalinity. The coating of shellac and castor oil has been found to digest in the intestinal fluids whether neutral or slightly acid, and is a reliable coating.

4. There was evidence that small capsules passed out of the stomach much more uniformly and within a shorter period of time than did the large capsules.

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THE QUANTITATIVE DETERMINATION OF VOLATILE OILS IN VEGETABLE DRUGS.*

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Methods for the determination of the volatile oil content of vegetable drugs usually depend (*a*) upon extraction with a solvent; (*b*) upon distillation with water or steam or (*c*) upon a combination of the two methods. The literature in many cases, describes comparative studies of two methods, with the usual conclusion that the method giving the higher percentage result is the preferable one; but as these determinations were always run on samples of drugs, such a conclusion is inconsistent, since the volatile oil content of the drugs used was an unknown quantity. While one method may give results consistently higher than the other, the analyst never knows which result more closely approximates the actual amount of volatile oil present in the drug.

In order to make a critical study of various methods for the determination of the volatile oil content of vegetable drugs, purified and thoroughly oven-dried sawdust was impregnated with known quantities of volatile oil, of moisture, or of volatile oil and moisture. The impregnation was carried out in capped wide-mouth jars having a hole in the cap large enough to admit the nozzle of a fine-spray atomizer. The volatile oil or moisture was sprayed onto the sawdust with accompanying agitation of the jar to insure uniform impregnation. The weight of the dry sawdust was known and the atomizers were weighed before and after spraying. In using samples of this type the accuracy of any method studied may be gaged by the proximity of the final result to the actual amount of volatile oil, of moisture, or of both employed at the beginning. Artificially prepared samples of this type are, of course, not exactly similar to crude drugs, but they approximate them as closely as is experimentally possible. By using these samples each step in any method can be studied critically and any fallacies or manipulative errors can readily be determined. A number of methods have been studied in this manner.

VOLATILE ETHER EXTRACTIVE METHOD.

This method has been official for several decades and appears again in the U. S. P. XI (page 475). It consists, in brief, of (*a*) drying the drug over sulfuric acid for twelve hours; (*b*) extracting with absolute ether continuously for twenty hours; (*c*) evaporating the ether spontaneously; (*d*) drying the extract eighteen hours over sulfuric acid; (*e*) weighing and (*f*) heating gradually to constant weight at 110° C. The loss in weight is volatile oil.

Several sources of error may be present in this process: (1) It is doubtful whether the drying in (*a*) and (*d*) is sufficient. If water be present in the drug it would be extracted and added to the final loss in weight. (2) Even though absolute ether is used in the extraction process, a considerable amount of moisture may condense from the air when the ether is evaporated spontaneously (*c*). With resinous drugs there is a considerable amount of "scumming over" and the varnish-like skin may hold both moisture and ether beneath it. These will volatilize during the

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final heating and will thus be calculated as volatile oil. (3) There may be a loss of volatile oil in the desiccator (*d*) and also a loss during the spontaneous evaporation (*c*). (4) Some decomposition of constituents other than volatile oil may occur during the heating process (*f*).

EFFICIENCY OF DESICCATORS IN REMOVING MOISTURE.

Anhydrous sawdust in which moisture was uniformly incorporated was dried over calcium chloride and over sulfuric acid in both large (average capacity 2650 cc.) and small (average capacity 680 cc.) desiccators. The samples were weighed at time intervals to note the loss in weight. The moisture content of the sawdust, before placing in the desiccators, was determined on duplicate samples by heating at 110° C. to constant weight.

Sawdust Moisture Content: 10.8%.

Desiccants: Fresh.

Percentage of Total Moisture Lost:	Small $CaCl_2$.	Large $CaCl_2$.	Small H_2SO_4.	Large H_2SO_4.
In 24 hours	77.7%	78.6%	99.2%	87.5%
In 2 days	88.4%	85.1%	98.2%	86.5%

Sawdust Moisture Content: 10.4%.

Desiccants: 3 to 4 Weeks in Use.

Percentage of Total Moisture Lost:	Small $CaCl_2$.	Large $CaCl_2$.	Small H_2SO_4.	Large H_2SO_4.
In 24 hours	49.5%	54.1%	47.9%	47.4%
In 2 days	75.9%	69.7%	68.6%	67.9%
In 3 days	83.2%	75.9%	80.9%	75.7%

Sawdust Moisture Content: 4.85%.

Percentage of Total Moisture Lost:	Small $CaCl_2$.	Large $CaCl_2$.	Small H_2SO_4.	Large H_2SO_4.
In 24 hours	55.7%	61.9%	53.6%	63.9%
In 2 days	72.1%	70.1%	70.1%	76.3%
In 3 days	80.4%	82.4%	78.7%	86.6%

NOTES.

(1) The drying was not nearly complete at the end of twenty-four hours in the desiccators, except in one case: the freshly prepared, small H_2SO_4 desiccator. It may be assumed that a drug containing 5% to 10% of moisture is never fully dried in a desiccator in twelve hours.

(2) Neither the size of the desiccator nor the type of desiccant appear to materially affect the results. The average percentage of desiccation at the end of 24 hours over calcium chloride is 62.9%, and over sulfuric acid 66.6%; in the small desiccators 63.9%, and in the larger desiccators 65.7%.

(3) The fresh desiccants show a much greater drying power, especially during the first day, over the desiccants that had been in use several weeks.

LOSS OF VOLATILE OIL IN DESICCATORS.

Anyone familiar with the volatile ether-soluble extractive method has observed that when drying volatile oil drugs over sulfuric acid, there is a rather rapid darkening of the acid indicating the presence of organic matter; probably lost volatile oil. The following tables are illustrative of the amount of volatile oil lost from evaporating dishes standing in various desiccators at room temperature. The desiccators are the same as used in the previous work.

Oil of Eucalyptus (Sp. Gr. 0.905).

Per Cent of Total Volatile Oil Lost:	Small $CaCl_2$.	Large $CaCl_2$.	Small H_2SO_4.	Large H_2SO_4.
In 24 hours	94.5%	95.0%	94.9%	42.8%
In 2 days	95.2%	96.2%	97.4%	68.2%
In 5 days	95.2%	96.4%	98.0%	86.3%
In 7 days	95.0%	96.4%	98.2%	96.7%
In 8 days	95.8%	96.6%	98.8%	96.8%

Oil of Clove (Sp. Gr. 1.050).

Per Cent of Total Volatile Oil Lost:	Small $CaCl_2$.	Large $CaCl_2$.	Small H_2SO_4.	Large H_2SO_4.	Small $Mg(ClO_4)_2$.
3rd day	5.2%	5.6%	5.9%	6.1%	5.8%
4th day	5.6%	6.4%	9.0%	6.5%	6.4%
6th day	6.8%	7.7%	8.3%	7.9%	7.7%
7th day	7.1%	8.1%	8.7%	8.4%	8.2%
10th day	10.1%	11.1%	11.6%	11.3%	11.1%

Pinene (Sp. Gr. 0.895).

Per Cent of Total Volatile Oil Lost:	Small $CaCl_2$.	Large $CaCl_2$.	Small H_2SO_4.	Large H_2SO_4.	Small $Mg(ClO_4)_2$.
1st day	27.8%	32.4%	41.8%	86.4%	39.4%
4th day	64.9%	79.5%	86.5%	88.1%	92.1%
5th day	72.9%	86.9%	87.7%	88.3%	92.8%
7th day	82.0%	89.2%	88.5%	88.4%	93.0%
8th day	84.5%	89.9%	88.7%	88.4%	93.6%

Oil of Chenopodium (Sp. Gr. 0.950).

Per Cent of Total Volatile Oil Lost:	Small $CaCl_2$.	Large $CaCl_2$.	Small H_2SO_4.	Large H_2SO_4.
1st day	3.7%	4.0%	3.6%	4.0%
2nd day	6.6%	7.1%	8.5%	7.4%
5th day	12.3%	13.5%	22.8%	14.8%
6th day	13.9%	15.3%	26.4%	17.5%
7th day	15.6%	16.8%	29.6%	21.5%

NOTES.

(1) Volatile oils in evaporating dishes do not completely simulate drugs (volatile oil in cellular tissue), yet it is very evident that some volatile oil may be lost from the drug, during the preliminary drying of the drug in the desiccator before the ether extraction.

(2) The rate of evaporation of volatile oils in desiccators seems to be a function of the specific gravity; that is, the lower the specific gravity of the oil the more rapid the rate of evaporation. The rate of evaporation is, of course, a function of the vapor pressures of the oil constituents and the relation between the rate of evaporation and the specific gravity should be considered in the light of being a coincidence rather than fixed rule.

(3) The size of the desiccator and the nature of the desiccant appear to have little effect on the rate of evaporation. The larger desiccators with sulfuric acid are perhaps slightly more effective.

(4) It seems very evident that volatile oil must be lost during the desiccation of the ether extract after the ether has been spontaneously evaporated.

EXTRACTION OF VOLATILE OIL-SAWDUST MIXTURES BY THE OFFICIAL METHOD.

Known quantities of volatile oils absorbed by sawdust were extracted by the U. S. P. method for volatile ether-soluble extractive. After the ethereal solution was evaporated spontaneously and the extract dried over sulfuric acid for eighteen hours, the total ether-soluble extractive weighed much less than the original weight of the oil taken. After heating the total ether-soluble extractive at 110° C. to constant weight, the total loss in weight (volatile ether-soluble extractive) calculated on the original weight of the oil was noted.

	Original Weight of Oil Taken.	Loss during Evaporation and Desiccation.	Loss on Heating at 110° C.	Efficiency of Official Method.
Oil of Eucalyptus	0.2136 Gm.	0.2013 Gm.	0.0123 Gm.	5.77%
Oil of Peppermint	0.2821 Gm.	0.2350 Gm.	0.0471 Gm.	16.71%
Pinene	0.2457 Gm.	0.1279 Gm.	0.1178 Gm.	47.94%
Oil of Clove	0.2941 Gm.	0.0490 Gm.	0.2450 Gm.	83.30%
Oil of Chenopodium	0.2163 Gm.	0.0241 Gm.	0.1922 Gm.	88.85%

NOTES.

(1) The efficiency of the official method for determining volatile ether-soluble extractive is the percentage of loss in weight on heating at 110° C. as compared with the original weight of the oil.

(2) The loss in weight of volatile oil during evaporation and desiccation again bears a fair ratio to the specific gravity of the oil; the lower the specific gravity, the greater the loss. Here again, too much weight should not be placed upon this relationship.

(3) While the volatile oil-sawdust mixtures do not exactly simulate drugs (no resin being present and usual "scumming over" being absent) there is never-the-less definite evidence that considerable error may occur.

DISTILLATION METHODS.

D. A. B. Method.—The German Pharmacopœia VI was the first pharmacopœia to officially introduce a distillation method for the determination of volatile oils in drugs. In this method the drug material is distilled with water, the distillate (volatile oil and water) being caught in a separatory tunnel; NaCl is then added to the contents of the separatory funnel, and the oil removed by shaking with pentane. The pentane extracts are evaporated at low heat, the volatile oil residue dried in a desiccator for *half an hour* and weighed. Preliminary experiments show this method to be subject to errors similar to those found in the volatile ether-soluble extractive method: (*a*) insufficient drying and (*b*) loss of volatile oil in desiccator.

Criticisms of this method agreeing with our own findings have been published in the literature (1). The further investigation of this method has been deferred for the present.

Clevenger Method.—In 1927 Clevenger (2) introduced a volatile oil trap, so designed that the distilled volatile oil remains in the trap and the water is returned to the continuously boiling flask containing the drug and water mixture. That part of the trap retaining the oil is calibrated and volume readings can be made directly at any time during the progress of the distillation. The method has much to commend it, especially its simplicity. It is further advantageous in that the oil can be removed from the trap, and its constants (specific gravity, optical rotation, refractive index, etc.) determined.

The method is somewhat disadvantageous from the standpoint of the large sample of drug material that must be used. In order to eliminate experimental error a yield of from 1 to 2 cc. of oil should be obtained. Since many drugs contain less than 1% of volatile oil, this means that a sample of 100 Gm. or more must be used for one determination.

Experiments employing several volatile oils were conducted with this apparatus using 1 cc. or 2 cc. of oil, 50 Gm. of purified anhydrous sawdust and 200 cc. of water.

Modifications of the method were attempted, such as omitting the sawdust and simply mixing the volatile oil with the water; employing various concentrations of brine in place of water; and varying the type of condenser used. The final readings were usually about 10% lower than the amount of volatile oil taken.

Exp. No.	Quantity and Oil Used.	Sawdust.	Salt.	Final Reading.	Per Cent Efficiency.
(*a*)	1 cc. Eucalyptus	50 Gm.	....	0.90 cc.	90.0%
(*b*)	2 cc. Eucalyptus	50 Gm.	....	1.80 cc.	90.0%
(*c*)	2 cc. Peppermint	50 Gm.	....	1.80 cc.	90.0%
(*d*)	2 cc. Pepermint	50 Gm.	60 Gm.	1.85 cc.	92.5%
(*e*)	2 cc. Lavender	50 Gm.	....	1.80 cc.	90.0%
(*f*)	2 cc. Pinene	50 Gm.	....	1.80 cc.	90.0%
(*g*)	2 cc. Pinene	....	....	1.80 cc.	90.0%
(*h*)	2 cc. Pinene	....	....	1.90 cc.	95.0%
(*i*)	2 cc. Pinene*	....	60 Gm.	1.85 cc.	92.5%
(*j*)	2 cc. Pinene	....	....	1.80 cc.	90.0%
(*k*)	2 cc. Pinene	....	60 Gm.	1.80 cc.	90.0%
(*l*)	2 cc. Pinene	....	30 Gm.	1.80 cc.	90.0%
(*m*)	2 cc. Cinnamon	50 Gm.	....	1.85 cc.	92.5%
(*n*)	2 cc. Clove	50 Gm.	....	1.95 cc.	97.5%
(*o*)	2 cc. Clove	....	30 Gm.	1.90 cc.	95.0%
(*p*)	2 cc. Chenopodium	....	....	1.50 cc.	75.0%
(*q*)	2 cc. Chenopodium	....	30 Gm.	1.75 cc.	87.0%
(*r*)	2 cc. Chenopodium	....	30 Gm.	1.80 cc.	90.0%
(*s*)	2 cc. Chenopodium*	....	30 Gm.	1.80 cc.	90.0%
(*t*)	2 cc. Chenopodium*	....	30 Gm.	1.80 cc.	90.0%

* Water used was the saturated water remaining after a previous distillation.

NOTES.

(1) (*j*) and (*k*) were run with the usual type of reflux condenser; all others with the ball-type condenser.

(2) (*m*), (*n*) and (*o*) were run with the trap designed for oils heavier than water. With this type of apparatus the oil is transferred from the trap to a graduated cylinder. The trap is then washed with ether, the ether evaporated and the residual oil added to the graduated cylinder. The use of ether here may involve a slight source of error.

(3) Two possibilities of error are suggested, namely:

(*a*) The oil may remain in solution in the water; then the use of oil-saturated water and of brine should indicate an improvement in results and possibly they do.

(*b*) The last traces of oil may be non-distillable because of physical reasons, such as vapor density.

(4) The method is certainly a marked improvement over the present official method in that (*a*) it is simple in operation; (*b*) it consumes much less time; (*c*) it actually yields the volatile oil and its constants can be checked; and (*d*) it gives far more accurate results.

Mijnhardt Method.—In 1936 Mijnhardt published a method (1) employing a microtrap. In this case the trap is located within the neck of a Kjeldahl flask used for boiling the drug-water mixture. The trap is simply the lower part of the condenser, the oil being drawn down into the lower constricted portion of the trap after distillation. This constricted portion is graduated into 0.02-cc. units. With this method smaller samples (5 to 10 Gm.) of drug material may be used.

Several experiments employing various oils gave a loss of from 10% to 30% of volatile oil. When a brine mixture is used in place of water, care must be used regarding the concentration of the brine. If this is too high the boiling point will be

raised high enough to cause the water in the trap (which is located within the flask) to boil and thus ruin the results.

Results with the Mijnhardt apparatus were as follows:

Exp.	Quantity and Oil Used.	Sawdust.	Salt.	Final Reading.	Per Cent of Efficiency.
(*a*)	0.2 cc. Lavender	20 Gm.	....	0.14 cc.	70%
(*b*)	0.2 cc. Lavender	20 Gm.	60 Gm.	0.09 cc.	*
(*c*)	0.2 cc. Lavender	20 Gm.	30 Gm.	0.17 cc.	85%
(*d*)	0.2 cc. Pinene	....	....	0.15 cc.	75%
(*e*)	0.2 cc. Pinene**	....	....	0.16 cc.	80%
(*f*)	0.2 cc. Pinene	....	30 Gm.	0.18 cc.	90%
(*g*)	0.2 cc. Chenopodium**	....	30 Gm.	0.18 cc.	40%
(*h*)	0.2 cc. Chenopodium**	....	30 Gm.	0.10 cc.	50%

* The brine concentration in (*b*) was high enough to raise the temperature of the water in the trap above the boiling point and thus cause an error.

** Water used was the saturated water remaining after a previous distillation.

NOTES.

(1) To adapt this method to oils heavier than water, a known quantity of pinene is added to the drug, and subsequently subtracted from the total volume of oil in the trap. (Mijnhardt includes a volume shrinkage factor.)

(2) The method has certain favorable features but the losses are unduly large.

(3) Sometime after the completion of our work van Giffen published a paper (3) in which he points out errors in the Mijnhardt method which agree with our findings.

Wasicky Method.—In 1933 Wasicky (4) published a distillation method utilizing a flask for generating steam, in the upper compartment of which is a chamber containing the drug. In this method the drug is not in contact with the water. The distillate is caught in a separatory funnel at the lower end of which is a calibrated microburette. The oil is removed from the water in the separator by shaking with a carefully measured volume of dekalin, the whole inverted, the dekalin-oil mixture allowed to rise into the microburette and the volume read.

This method and apparatus have many features which commend it in a theoretical way, but we have been unfortunate in our failure to master the technique. The dekalin-oil mixture did not quantitatively rise into the microburette, but remained adherent to the sides of the separator. Repeated cleansing with sulfuric acid-dichromate cleaning solution failed to overcome the difficulty. We hope to take the matter up with Dr. Wasicky and learn to improve our technique.

Aside from manipulative difficulties it should also be mentioned that the apparatus is rather complex, somewhat costly and rather fragile.

DRYING METHODS.

Oven Method.—The U. S. P. XI gives directions for the determination of moisture in drugs containing ether-soluble constituents volatile at 100° C. (5) which the total loss in weight at 100° C. is determined on one sample; the volatile-ether extractive being determined on a second sample and subtracted from the total loss in weight upon heating, the difference being the moisture. A reversal of this process suggested itself and we have named it the oven method.

In this method a sample of the drug is placed in an oven and heated to constant weight at 100° C. This loss represents total volatile matter. The amount

of moisture is determined in a second sample by the toluene method of the U. S. P. XI. This figure subtracted from the total volatile figure represents the amount of volatile matter other than water.

A measured amount of volatile oil and water were carefully mixed with anhydrous sawdust and the above procedure was used for determining each. The following table illustrates the results obtained:

	Measured Quantity.	Determined Quantity.
Moisture	6.1 %	6.0% (Toluene method)
Oil of Clove	5.9 %	6.3%
Total	12.0 %	12.3% (Oven method)
Moisture	6.5 %	6.6% (Toluene method)
Pinene	5.06%	5.0%
Total	11.56%	11.6% (Oven method)
Moisture	6.1 %	6.0% (Toluene method)
Oil of Chenopodium	5.9 %	6.3%
Total	12.0 %	12.3% (Oven method)

NOTES.

As was anticipated, this method gave excellent results with the sawdust-volatile oil-moisture samples. It has much to commend it both from the standpoint of simplicity and from the absence of the sources of error so evident in other methods. When applied to actual drug evaluation there are, however, certain factors which may give rise to error. There is evidence in certain drugs of the presence of constituents (not volatile oils) which decompose at even as low a temperature as 100° C. In such cases the total loss in weight would represent more than just volatile oil and moisture.

OTHER METHODS.

Other methods appear in the literature but these invariably depend upon the same principles involved in the methods studied above, and are subject to the same errors. As this part of our work is brought to a close van Giffen (3) publishes a new method involving extraction with petroleum ether (under a reflux condenser) after which the petroleum ether is concentrated at 50° C., distilled with steam and the distillate shaken with petroleum ether, which is again concentrated at 50° C., dried with sodium sulfate and finally concentrated in a current of air, the residual volatile oil determined by weighing. While this method has not been investigated experimentally many sources of error suggest themselves.

SUMMARY.

1. A critical examination of the official method for volatile ether-soluble extractive reveals several sources of error, namely:

(*a*) The removal of the moisture from the drug kept in the desiccator for 12 hours apparently is difficult of accomplishment. Sawdust containing a known quantity of moisture and kept in various sizes of desiccators and with various desiccants showed an average percentage of desiccation of 65% after 24 hours and 83% after 2 to 5 days.

(*b*) Loss of volatile oil during the evaporation and desiccation of the ether extraction is certain. Volatile oils in dishes in various desiccators and over various desiccants showed an average loss of 33% in 24 hours and losses of from 10% to 98.8%, after several days. The rate of evaporation depends on the vapor pressure and possibly on the specific gravity of the oil.

(*c*) Even if absolute ether is used for the extraction process, moisture may condense from the air when the ether is spontaneously evaporated, collect in the extract and constitute a part of the calculated volatile extractive.

(*d*) Decomposition of constituents other than volatile oil during the heating process may occur.

2. Comparative studies of methods for volatile oil determination run on drug samples, and with the usual conclusion that the method giving the highest percentage of results is the preferable one, may be inconsistent, since the volatile oil content of the drugs used was an unknown quantity.

The official method run on samples of purified, anhydrous sawdust containing known quantities of volatile oil gave results showing from 5.77% to 88.85% efficiency. The quotient of efficiency is the percentage of loss in weight on heating at 110° C. as compared with the original weight of the oil taken.

3. Several distillation methods, namely, the D. A. B. Method (German Pharmacopœia VI), Clevenger Method, Mijnhardt Method and Wasicky Method were carefully tried out. The D. A. B. method has about the same faults as the U. S. P. method; the Mijnhardt method gave us a low efficiency; and we were not able to satisfactorily develop the technique of the Wasicky method. Both the Mijnhardt and Wasicky methods use a microburette and theoretically they seem to have good possibilities. The Clevenger method is accurate to at least 90%, is simple, easily read, rapid and yields the actual volatile oil in sufficient quantity to check its constants.

4. The simple oven method suggests itself as being of real practical value. It is simple in operation, saving of time, requires no complex apparatus and presents no manipulative difficulties. It certainly yields far more accurate results than the present official volatile ether-soluble extractive method. The total volatile matter is determined by heating at 100° and from this is subtracted the moisture determined by the toluene distillation method, the difference being volatile oil.

The only error which suggests itself involves the possibility of products present in drugs (other than volatile oil) which might decompose during the heating at 100° and thus cause the total volatile matter to represent more than just volatile oil and moisture. It is proposed to demonstrate the usefulness of this method by running it upon samples of drugs and checking its results against the Clevenger method, which appears to be accurate to 90%. If these results run uniformly about 10% higher than those obtained with the Clevenger method its usefulness will have been demonstrated. If on the other hand they run considerably higher than the Clevenger results, the loss in weight due to decomposition of non-volatile oil constituents in the drugs, will indicate its impracticability.

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(5) U. S. P. XI, page 473, Paragraph 11.

SALTS OF SHIKIMIC ACID AND DERIVATIVES.*

II. SALTS OF AMMONIUM AND SUBSTITUTED AMMONIAS.**

BY HSING-HAN LEI.

If, as previously stated, the isolation of crystalline salts, notably of the alkali metals, may possibly be interfered with by the presence of the three hydroxy groups in shikimic acid, ammonium hydroxide apparently does not cause such interference. Results with other nitrogen basis were not always as favorable.

Ammonium Shikimate.—This was first prepared by Eykman[1] in 1891 and described by him. It was also prepared by S. Y. Chen[2] in 1929. Repetition of these experiments yielded satisfactory results.

Analysis: (By Kjeldahl method.)

1. 0.2125 Gm. of substance required 11.09 cc. of 0.1N HCl = 7.23 p. c. of N.
2. 0.3055 Gm. of substance required 11.22 cc. of 0.1444N HCl = 7.36 p. c. of N.

The theoretical percentage of nitrogen of the formula $C_6H_6(OH)_3COONH_4$ is 7.33 p. c.

Methylamine Shikimate.—This was prepared by S. Y. Chen in 1929,[3] m. p. given was 162°. Repetition of his experiment yielded a compound with m. p. 163–164°.

n-Propylamine Shikimate.—This was prepared as follows: An excess of alcoholic propylamine solution was refluxed on a water-bath with alcoholic shikimic acid for about two hours. After the removal of most of the solvent by evaporation a thick sticky syrup was obtained which could not be crystallized.

n-Amylamine Shikimate.—This was prepared like the propylamine salt and yielded unsatisfactory results.

Benzylamine Shikimate.—This was made from a hot alcoholic mixture of shikimic acid and benzylamine. The reaction took place immediately. It crystallized in white needles from alcohol. M. p. 195–196°.

Nitrogen determinations according to the Kjeldahl method gave the following results:

1. 0.2825 Gm. of substance required 7.25 cc. of 0.1444N HCl = 5.19 p. c. N.
2. 0.3352 Gm. of substance required 8.3 cc. of 0.1444N HCl = 5.01 p. c. N.

Calculated for $C_6H_6(OH)_3\,COO.HN_3.CH_2\,C_6H_3$ ..... 4.98 p. c.
$C_6H_6(OH)_3CO.NH.CH_2\,C_6H_3$ ..... 5.33 p. c.

Ephedrine Shikimate.—Equivalent amounts of shikimic acid and ephedrine were refluxed on a water-bath with 95 p. c. alcohol as solvent for about half an hour. Upon cooling the shikimate crystallized out as large crystals. They can be purified by recrystallizing from alcohol. M. p. 162–163°.

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* Continued from JOUR. A. PH. A., 26, 902 (1937).

** From the laboratory of Edward Kremers.

[1] *Ber.*, 24, page 1281. For a crystallographic study of the large crystals obtained from water see Groth, *Chemische Krystallographie*, 3, page 635.

[2] *Am. J. Pharm.*, 101, page 689.

[3] *Ibid.*, 101, page 691.

Analysis: The determination of nitrogen was carried out by the Dumas method:

1. 0.2093 Gm. gave 8.5 cc. of N at 24° and 742.4 mm. = 4.46 p. c. N.
2. 0.1040 Gm. gave 4.3 cc. of N at 25° and 738 mm. = 4.49 p. c. N.

Calculated as addition product $C_{10}H_{15}ON.C_6H_6(OH)_3COOH$, N = 4.13 p. c.
Calculated as condensation product $C_{10}H_{15}ON.C_6H_6(OH)_3COOH$, N = 4.53 p. c.

Because elementary analysis did not seem satisfactory on account of the large molecule of ephedrine shikimate, the salt was resolved into its components. The ephedrine was determined by the U. S. P. XI method (page 146) for the assay of ephedrine sulfate, the shikimic acid gravimetrically as its ammonium salt.

0.5-Gm. sample yields 0.24286 Gm. of ephedrine (10.3 cc. of 0.09972N NaOH was used for titrating back of 20 cc. 0.1249N HCl or 14.71 cc. of $N/10$ HCl used for titrating the base liberated) and 0.2811 Gm. of ammonium shikimate, corresponding to 48.57 p. c. of ephedrine and 51.22 p. c. of shikimic acid, respectively.

Calculated for $C_{10}H_{15}ON.C_6H_6(OH)_3COOH$: Base = 48.67 p. c.; acid = 51.33 p. c.

Aniline Shikimate.—This was reported by S. Y. Chen in 1929[1] melting point given as 178°. Repetition of the experiment yielded a powder m. p. 194–195°. In aqueous solution it is acid to litmus paper.

Analysis gave the following results:

1. 0.245 Gm. of substance required 9.3 cc. of 0.1N HCl = 5.32 p. c. N.
2. 0.252 of substance required 9.6 cc. of 0.1N HCl = 5.33 p. c. N.

Calculated for $C_6H_6(OH)_3COO.NH_3.C_6H_5$ ..... 5.25 p. c.
$C_6H_6(OH)_3CONH.C_6H_5$ ..... 5.62 p. c.

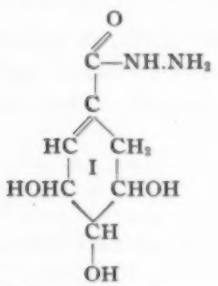
o-Toluidine Shikimate.—This was made by refluxing the alcoholic mixture of shikimic acid and base on a water-bath for one hour. The product was a powder. M. p. 178–180°.

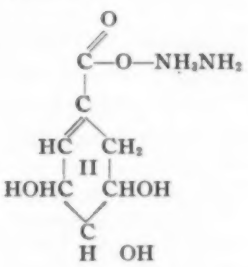
Analysis gave the following results:

1. 0.2035 of substance required 7.3 cc. of 0.1N HCl = 5.03 p. c. N.
2. 0.2145 of substance required 7.8 cc. of 0.1N HCl = 5.09 p. c. N.

Calculated for $C_6H_6(OH)_3COO.NH_3.C_6H_4.CH_3$ ..... 4.98 p. c.
$C_6H_6(OH)_3CONH.C_6H_4.CH_3$ ..... 5.33 p. c.

Hydrazine Shikimate.—In an attempt to produce a condensation product of hydrazine (I) with shikimic acid, an addition product (II) resulted.





[1] *Am. J. Pharm.*, 101, page 691.

When equivalent amounts of the two substances were mixed at room temperature a thick paste resulted with the evolution of appreciable heat. After heating for ten minutes on a water-bath, alcohol was added and the heat continued for an hour, supplemented by a mechanical stirrer. A white crystalline product resulted, m. p. 147–148°.

The nitrogen content was determined by the Dumas method.

1. 0.1045 Gm. yielded 13.1 cc. N at 30° and under 733-mm. pressure, corresponding to 13.14 p. c. N.
2. 0.1068 Gm. yielded 13.2 cc. N at 30° and under 743-mm. pressure, corresponding to 13.13 p. c. N.

	I.	II.
Computed for	14.89 p. c.	13.59 p. c.

Pyridine Shikimate.—This was prepared by S. Y. Chen in 1929,[1] m. p. 184°. Repetition of the experiment yielded microscopic plates m. p. 184–185°.

Analysis gave the following results:

1. 0.291 Gm. of substance required 11.01 cc. of 0.1N HCl = 5.30 p. c. N.
2. 0.3012 Gm. of substance required 11.8 cc. of 0.1N HCl = 5.49 p. c. N.

Calculated for $C_6H_6(OH)_3.COOHC_5H_5$..... 5.54 p. c.

Quinine Shikimate.—This was prepared as follows: Two grams of shikimic acid were dissolved in 10 cc. of water with the aid of heat. An excess of quinine base was then added, shaking until most of the base had gone into solution. The solution was filtered upon cooling. Quinine shikimate crystallized out as colorless needles. The salt can be crystallized from alcohol, 221–222°.

Analysis: By modifying the methods described in Jenkins and DuMez, "Quantitative Pharmaceutical Chemistry," page 297, the base was determined gravimetrically.

1. 0.3666-Gm. sample yielded 0.2382 Gm. quinine corresponding to 64.97 p. c.
2. 0.3604-Gm. sample yielded 0.2335 Gm. quinine corresponding to 64.80 p. c.

The calculated amount for $C_6H_6(OH)_3COOH.C_{20}H_{24}O_2N_2$ is 65.08 p. c.

Quinidine Shikimate.—This salt was prepared like that of quinine. From diluted (60 p. c.) alcohol it was obtained in colorless needles, m. p. 224–226°.

When heated on an air-bath for four hours at a temperature of between 100° and 110° it did not lose in weight, indicating the absence of water of crystallization. The melting point of the salt thus treated was 225–226°.

Because of the large molecule, elementary analysis did not seem satisfactory. Hence it was resolved into its components. The quinidine was determined by the U. S. P. XI method (page 126) for the assay of codeine phosphate; the shikimic acid gravimetrically as its ammonium salt.

0.56 Gm. yielded 0.3650 Gm. of quinidine and 0.2162 Gm. of ammonium shikimate, corresponding to 65.18 p. c. of quinidine and 34.97 p. c. of shikimic acid, respectively.

Calculated for $C_{20}H_{24}O_2N_2.C_6H_6(OH)_3COOH$: Base = 65.08 p. c.; acid = 34.92 p. c.

Codeine Shikimate.—This salt was prepared like those of quinine and quinidine. From dilute alcohol it was obtained in crystals somewhat resembling cubes, m. p. 173–174° (sintered at 160°).

[1] *Am. J. Pharm.*, 101, page 691.

The analysis was carried out by the Dumas method:

1. 0.1015 Gm. gave 2.9 cc. N at 738.6 mm. and 27.5° = 3.06 p. c. N.
2. 0.1005 Gm. gave 2.9 cc. N at 738 mm. and 28° = 3.04 p. c. N.

Calculated for $C_{15}H_{21}O_3N.C_6H_6(OH)_3COOH$ ..... 2.96 p. c.

Strychnine Shikimate.—This was prepared from the strychnine base and aqueous shikimic acid as carried out in the preparation of the quinine salt. The salt crystallized out as colorless long plates, m. p. 234–236° (sintered at 154°).

Analysis: This was carried out as for quinine shikimate except that chloroform was used instead of ether as the extracting solvent.

1. 0.1075-Gm. sample yielded 0.078 Gm. strychnine corresponding to 72.5 p. c.

Calculated for $C_6H_6(OH)_3COOH.C_{21}H_{22}O_2N_2.2H_2O$ is 75.63 p. c.

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TOXICITY IN THE LEAVES OF RHODODENDRON CALIFORNICUM, HOOK. I.*

BY F. A. GILFILLAN AND CHIEKO OTSUKI.[1]

Since the days of Xenophon, in the fifth century B. C., it has been known that certain rhododendrons were poisonous, but all systematic investigation (1) of this toxicity dates since 1885, during which period research has been carried out on 15 species, of which 13 were found to contain poison.

Rhododendron californicum, which abounds in the forests of northern California and of western Oregon, Washington and British Columbia, was not one of the 15 species investigated. Although various botanical handbooks (15) state that the plant is said to be poisonous, no reference was found in the literature to any research on that particular species. The following report represents a preliminary investigation on the toxicity of this rhododendron.

EXPERIMENTAL.

Materials.—Leaves were collected in June 1935, and also in December 1936, along the Oregon coast near Newport and near Florence. Both samples were immediately air-dried indoors, losing about 58% of their weight during the curing. The dried leaves still contained about 16.4% of moisture, corresponding to 64.9% in the green leaves. The ash content was about 2.9% on the cured leaves, corresponding to about 1.2% in the green state.

Extraction with Alcohol.—Three different concentrations of alcohol, 15%, 45% and 95% were employed in extracting the ground dried leaves. The yields were 37%, 44.5% and 35%, respectively, but from the dried extract so produced, no crystalline substance could be obtained, nor other material with marked physiological activity, wherefore the method was abandoned. It is

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* Presented before the Scientific Section, A. PH. A. meeting, New York, 1937.

[1] Abstracted from a thesis presented by Chieko Otsuki in partial fulfilment of the requirements for the degree of Master of Science from the Oregon State College.

possible that the procedure might have been successful had it been employed on larger quantities than were used.

Extraction with Water.—Of the various aqueous extraction methods tried, the following appeared to be the best procedure. About five gallons of water were brought to boil in a large kettle, and 1000 Gm. of dried leaves were slowly added, boiling being maintained, and continued for half an hour after all leaves were added. After cooling, the liquor was decanted and evaporated to dryness, yielding 51.9% of extract "L," based on dried leaves.

Purification with Lead Acetate.—Of the above dried extract "L," 78 Gm. were dissolved in water, treated with excess 10% neutral lead acetate solution, filtered, saturated with hydrogen sulfide gas, again filtered and the filtrate concentrated. From the thick greenish liquid there separated a crop of greenish yellow crystals, "N." After washing with water, these weighed 1.827 Gm., representing 1.22% of the weight of the dried leaves, or 0.51% of green leaves. Concentrated sulfuric acid turned these crystals red, the color becoming more intense on warming. When diluted and made alkaline, the color disappeared, but reappeared on acidification. The crystals did not reduce Fehling's solution, before or after hydrolysis. When recrystallized, either from water or from normal butyl alcohol, they showed a melting point of 183.4° C. (corr.). They contained no nitrogen. Combustion showed them to consist of 55.7% of carbon and 7.34% of hydrogen, indicating an empirical formula of C_2H_3O. The molecular weight determination on this substance "N" is reported below.

Purification with Magnesium Oxide.—With 295 Gm. of the dried extract "L" were mixed 300 Gm. of heavy magnesium oxide and sufficient water to form a paste. After drying and pulverizing, the resultant 624-Gm. mix was extracted with two liters of 95% alcohol, warming and stirring for two hours. After standing over night, the alcohol was decanted, and 750 cc. additional alcohol were added to the powder, this second extraction being handled as before. When the combined alcoholic extracts were concentrated, amber-colored crystals were produced, weighing 8.8 Gm. and representing 1.55% of the dried leaves, or 0.65% of green leaves. Color reactions with various reagents were similar to those of the "N" crystals, but there was a slight reduction of Fehling's solution, due possibly to some impurity. After recrystallization from water, leaving the mother liquor "O," the crystals were almost white. Several determinations of the melting point of these "M" crystals, alone and in mixtures with the "N" crystals, showed them to be identical.

Molecular Weight Determinations.—It was first attempted to determine the molecular weight of the crystals "N" by the depression of the freezing point of water, but inconclusive results were obtained, varying from 199 to 319. Employing the boiling-point method in absolute alcohol for crystals "M" encountered more difficulty, as the samples were too small, and the results obtained were 321 and 401. When all crystals of "M" and "N" were mixed so as to secure a larger sample, results with 1.3488 Gm., 1.7865 Gm. and 2.2473 Gm. were 362, 365 and 349, respectively. If the value 344 be tentatively accepted, the formula for this substance would be $C_{16}H_{24}O_8$.

Toxicity.—A kilogram guinea pig was fed 4.8 Gm. of the extract "L," representing about 25 Gm. of green leaves. The animal died in 12 hours.

The crystals "M" were injected subcutaneously into two guinea pigs in amounts up to 33 mg., also the crystals were fed to three rabbits in amounts up to 150 mg., but none of the animals exhibited any toxic symptoms.

The mother liquor "O" from which these crystals had been obtained was next investigated. On evaporation of 1 cc. of this solution, there was obtained 0.1337 Gm. of a varnish-like residue. This amount, injected subcutaneously into a 435-Gm. guinea pig, caused retching and salivation in two minutes, and in 12 minutes, death. The heart was in diastole. Another guinea pig, weighing 475 Gm., when injected with 33 mg. of the material, showed the same symptoms, and died in 42 minutes. A rabbit weighing 1350 Gm. was fed 150 mg. of the substance, but showed no symptoms within 24 hours. It was then given 150 mg. subcutaneously, which produced convulsions in 14 minutes and death in 33 minutes.

SUMMARY AND CONCLUSIONS.

1. The dried leaves of *Rhododendron californicum*, Hook. were extracted with boiling water, and the extract purified by either of two processes.

2. From this poisonous extract was isolated a crystalline substance, analyzing as $C_{16}H_{24}O_8$, but devoid of toxic properties.

3. From the mother liquor of the crystals was obtained a resinous substance of high toxicity.

The investigation is being continued.

The authors are indebted to Mr. Claude Huggins of Springfield, Oregon, who provided most of the rhododendron leaves for this investigation, and to Mr. L. C. Britt, Chemist of the Oregon State Board of Pharmacy, who suggested several of the procedures used.

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AN ASSAY METHOD FOR TABLETS OF BELLADONNA EXTRACT.*

BY DALE T. WILSON.

Because of manipulative difficulties, the U. S. P. XI assay method for Extract of Belladonna is not applicable to tablets containing this extract. A modification of the U. S. P. XI assay method, involving the preliminary extraction of the alkaloids according to the shake-out method of the U. S. P. X, is somewhat more workable. However, the nature of tablet mixtures is such that rather stable emulsions are formed during the shake-out, with the result that assays are tedious and time-consuming. Furthermore, the final end-point in the titration is usually masked by the presence of chlorophyl and other colored extractive matter.

In an attempt to overcome these objectionable features the author has developed a method which appears to be quite satisfactory for the estimation of total alkaloids in Tablets of Belladonna Extract. The details of the procedure are given as follows.

Weigh not less than twenty tablets and determine the average weight. Powder and weigh accurately a sample equivalent to 25 grains of belladonna extract and transfer it to an extraction thimble having approximately a length of 94 mm. and an internal diameter of 33 mm. Place the extraction thimble in a medium size Soxhlet extractor and add about 125 cc. of ether in

* Chemical Control Laboratories, Eli Lilly and Company, March 10, 1938.

which has been dissolved 5 drops of hydrochloric acid. Extract for one hour, then discard this ether extract.

Now pour directly into the thimble in the Soxhlet extractor about 100 cc. of ether, which has been previously mixed with 7 cc. of stronger ammonia water. Stir the belladonna extract in the extraction thimble so that the ammonia comes in contact with all of the alkaloid. Add about 50 cc. of ether and extract for at least four hours, then apply a test to insure complete extraction.

Transfer the ether extract to a suitable separator and rinse the Soxhlet receiving flask with two 5-cc. portions of 2 per cent sulfuric acid, adding these acid washings to the separator. Extract the ether extract in the separator with four 10-cc. portions of 2 per cent sulfuric acid and collect these acid extracts in a second separator. Add an excess of stronger ammonia water to neutralize the acid extractions in the second separator and extract with 5 to 6 portions of chloroform or until the aqueous solution shows no test for alkaloids with Mayer's reagent. Filter the chloroform extracts into a 150-cc. beaker, evaporate to dryness on a water-bath and maintain at this temperature for fifteen minutes. Dissolve the residue in chloroform, evaporate to dryness on a water-bath, and continue the heating for fifteen minutes. Repeat this treatment for a third time. Dissolve the resulting residue in chloroform, add 5 cc. of $N/50$ acid, remove the chloroform by evaporation and titrate the excess acid with fiftieth normal sodium hydroxide, using a micro burette and methyl red as the indicator.

Each cc. $N/50$ acid = 0.00578 Gm. Belladonna Alkaloids.

DATA.

The results obtained in the assay of fourteen samples taken from three lots of belladonna extract tablets are given below. Percentages of the theoretical amount found are caculated on the basis of 1.25 per cent alkaloids of belladonna in Extract of Belladonna.

TABLE I.—TABLETS OF BELLADONNA EXTRACT, 1/8 GRAIN.

Assay Method Applied.	Sample in Grains of Belladonna Extract.	Number of Cc. $N/50$ Acid Required.	Percentage of the Theoretical Amount Found.
Proposed	25 grains	3.63 cc.	103.6%
Proposed	25 grains	3.65 cc.	104.1%
Proposed	25 grains	3.65 cc.	104.1%
Modified method of the U. S. P. X and XI	30 grains	4.36 cc.	103.7%
Modified method of the U. S. P. X and XI	30 grains	4.34 cc.	103.2%

TABLE II.—TABLETS OF BELLADONNA EXTRACT, 1/4 GRAIN.

Assay Method Applied.	Sample in Grains of Belladonna Extract.	Number of Cc. $N/50$ Acid Required.	Percentage of the Theoretical Amount Found
Proposed	25 grains	3.46 cc.	98.76%
Proposed	25 grains	3.49 cc.	99.62%
Proposed	25 grains	3.47 cc.	99.04%
Modified method of the U. S. P. X and XI	40 grains	5.61 cc.	100.10%
Modified method of the U. S. P. X and XI	40 grains	5.57 cc.	99.37%

TABLE III.—DISPENSING TABLETS OF BELLADONNA EXTRACT, 1 GRAIN.

Assay Method Applied.	Sample in Grains of Belladonna Extract.	Number of Cc. $N/50$ Acid Required.	Percentage of the Theoretical Amount Found.
Proposed	25 grains	3.61 cc.	103.0%
Proposed	25 grains	3.66 cc.	104.4%
Proposed	25 grains	3.63 cc.	103.6%
Modified method of the U. S. P. X and XI	40 grains	5.77 cc.	102.9%

COMMENTS.

By reducing the size of the assay sample to correspond with 25 grains of powdered extract the filtration during extraction of the alkaloids is considerably facilitated.

The first ether extraction, which is made in an acid medium, removes all of the available ether-soluble matter from the tablet sample, including much of the chlorophyl. Unless this material is removed the color of the indicator will be so masked in the titration as to make it difficult to determine the final end-point. This discarded ether extract has been found to yield negative results in the test for alkaloids. The alkaloids are then removed by ammoniacal ether extraction until complete exhaustion of the assay sample is obtained. The tablet filler remains behind with the exhausted drug and presents no difficulty in making subsequent extractions.

A distinctive advantage in the method is found in the fact that it requires a minimum amount of working time on the part of the analyst.

CONCLUSIONS.

1. A method is proposed for the assay of Tablets of Belladonna Extract which appears to be distinctly superior to a modified procedure based upon a combination of the U. S. P. X and the U. S. P. XI assay methods for Extract of Belladonna.

2. In principle this method may be advantageously applied to the determination of mydriatic alkaloids in other related pharmaceutical products.

I wish to acknowledge my indebtedness to Edward J. Hughes for his assistance in the preparation of this paper.

NOTE ON ASSAY OF CHLOROFORM LINIMENT, UNITED STATES PHARMACOPŒIA XI.*

BY SAMUEL W. GOLDSTEIN AND WILLIAM F. REINDOLLAR.

The method adopted by the Revision Committee of the United States Pharmacopœia XI for the determination of chloroform in chloroform liniment appears to be unnecessarily complicated, and in the hands of an inexperienced operator it is doubtful whether even approximate results would be obtained. Simpler procedures have been reported by Kunke (1) and Beal and Szalkowski (2).

Moraw (3) and Willgerodt (4) found that distillation methods applied to the determination of chloroform yielded low results. Beal and Szalkowski (2) used both the distillation and pressure bottle procedures and reported slightly lower results with the distillation method.

We found that, according to results obtained using the United States Pharmacopœia XI assay procedure, many of the commercial samples tested ran below the lower limit[1] prescribed for chloroform in chloroform liniment by the United States Pharmacopœia XI; therefore the following experiments were carried out.

* From the laboratories of the Bureau of Chemistry of the State of Maryland Department of Health.

[1] Since this work was completed the lower limit for chloroform in chloroform liniment was changed in the First Supplement of the United States Pharmacopœia XI from 40 Gm. to 35 Gm. of chloroform in 100 cc. of the liniment.

Reagents.—The reagents prescribed in the United States Pharmacopœia XI were used with the exception that nitric acid was employed in place of diluted nitric acid.

Chloroform Liniment.—A. 44.2347 Gm. (30 cc.) of chloroform U. S. P. (99.50%) were accurately weighed and made up to 100 cc. with soap liniment at 25° C.

B. 44.2926 Gm. (30 cc.) of chloroform U. S. P. (99.37%) were accurately weighed and made up to 100 cc. with soap liniment at 25° C.

In each case, except where noted, 10 cc. of the chloroform liniment was diluted to 100 cc. with alcohol. Determinations of chloroform were then made on these diluted solutions by the official procedure, and also by transferring 10 cc. directly into a pressure (or citrate) bottle containing 50 cc. of the alcoholic potassium hydroxide solution (3 in 10). When the pressure bottle method was used, the bottles and contents were placed in a wire basket which was set in a bath of cool water and covered with a towel. The water was then heated to boiling and maintained at that temperature for a half hour. The bottle was then cooled, the contents were transferred to a 500-cc. volumetric flask, and the official procedure was carried out from that point with the following exceptions. Kunke (1) found that it was unnecessary to evaporate the alcohol before acidifying with nitric acid preliminary to determining chloride by the Volhard method. After checking his results in several experiments this step was deleted. The use of nitric acid instead of diluted nitric acid was found to be necessary; inasmuch as the ferric ammonium sulfate T.S. colored the solution to such an extent that a sharp end-point could not be obtained in the titration. In certain cases the chloride was determined gravimetrically.

TABLE I.—RESULTS OBTAINED WITH STANDARD LINIMENT.

	U. S. P. XI Method.		Pressure Bottle Method. Volumetric.		Gravimetric.	
Sample.	Gm. Found/ 100 Cc.	% $CHCl_3$ Recovered	Gm. Found/ 100 Cc.	% $CHCl_3$ Recovered.	Gm. Found/ 100 Cc.	% $CHCl_3$ Recovered.
A	40.04	90.98	43.53	98.91	...	...
A	38.50	87.48	43.53	98.91	...	...
A	38.00	86.35	42.83	97.32	...	...
A	40.55	92.14	43.62	99.11	...	...
A	41.34	93.93	42.74	97.10	...	...
A	40.80	92.71	43.23	98.23	43.83	99.59
B	...	...	43.18	98.11	43.83	99.59
B	...	...	43.13	98.00	43.78	99.47
B	...	...	43.23	98.23	43.74	99.41
B*	...	...	43.58	99.02	43.83	99.59
B*	...	...	43.58	99.02	44.00	99.97

* In experiments Nos. 10 and 11, 1 cc. of chloroform liniment was measured with a 1-cc. pipette directly into pressure bottles containing 50 cc. of alcoholic potassium hydroxide.

The results indicate that with the pressure bottle method more accurate results are obtainable than when the official procedure is employed.

Proposed Method.—Place 50 cc. of alcohol in a 100-cc. volumetric flask, and measure exactly 10 cc. of chloroform liniment at 25° C. into the flask by means of a pipette, placing the tip of the pipette just beneath the surface of the alcohol. Make up to a volume of 100 cc. at 25° C. with alcohol, and mix thoroughly. Transfer 10 cc. of the alcoholic solution to a pressure (or citrate) bottle containing 50 cc. of an alcoholic solution of potassium hydroxide (3 in 10), holding the end of the pipette just above the alkali solution. Seal the bottle and place in a water-bath, heat the water to boiling and maintain at the boiling temperature for a half hour. Cool the mixture, and transfer it to a 500-cc. volumetric flask; rinse the reaction flask with distilled water, add the rinsings to the reaction mixture and finally add enough distilled water to make a volume of 500 cc. at 25° C. Mix the contents of the flask thoroughly and transfer a 100-cc. portion of the solution to a 250-cc. volumetric flask; then add a few drops of phenolphthalein T.S. and acidify with nitric acid, adding an excess of about 5 cc. of acid. Add 40 cc. of tenth-normal silver nitrate, shake until the precipitate coagulates, make up the volume with distilled water at 25° C. and mix thoroughly. Filter the supernatant liquid through a dry filter, rejecting the first 15 cc. of filtrate. Titrate 000

cc. of the filtrate with tenth-normal thiocyanate solution using 3 cc. of ferric ammonium sulfate T.S. as indicator. Carry out a blank determination, omitting only the chloroform liniment, and correct the volume of silver nitrate consumed in the assay by the volume consumed in the blank determination. Each cc. of tenth-normal silver nitrate is equivalent to 0.00398 Gm. of $CHCl_3$.

The following results were obtained with commercial samples run by the official procedure and the pressure bottle method.

TABLE II.—RESULTS EXPRESSED AS GM. OF $CHCl_3$ PER 100 CC.

Sample.	U. S. P. XI Method, Tinfoil on Cork Stopper.	U. S. P. XI Method, Tinfoil on Rubber Stopper.	Pressure Bottle Method.
1	35.47	37.11	41.34
2	28.06	37.76	40.30
3	...	32.14	34.18
4	...	33.98	40.99
5	...	40.99	43.48
6	...	36.47	38.95

DISCUSSION.

The proposed method eliminates distillation, the four-hour refluxing period, and a transfer of the reaction mixture; thereby decreasing the opportunity for error and at the same time greatly shortening the time required for the determination. Slightly higher results are obtained by the gravimetric modification of the recommended procedure.

SUMMARY.

1. A simpler and less time-consuming procedure for the assay of chloroform liniment is recommended.

2. The average recovery of chloroform by this procedure is 98.4 per cent.

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HYDROGENATED CASTOR OIL IN OINTMENTS.—PART II COSMETICS.*

BY GEORGE W. FIERO AND LAURENCE D. LOCKIE.[1]

Solidifying agents employed in cosmetics are chiefly waxes such as white beeswax, spermaceti, paraffin, ceresin, etc. Waxes differ from true fats in that they are not saponifiable (*i. e.*, not glycerides of fatty acids) and supposedly are not as readily absorbed by the skin. The use of animal fats, such as lard, is unsatisfactory because of the tendency to rancidity.

Hydrogenated castor oil was found satisfactory as a base for ointments (1). Since ointments are closely related to many cosmetics, the use of the oil as a substi-

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tute for waxes was investigated. Hydrogenated castor oil may be prepared with any desired melting point up to about 86° C. For certain cosmetics, a lower melting point oil might be used. However, the tendency to rancidity varies with the extent of hydrogenation, completely hydrogenated castor oil not being susceptible to rancidity. Partially hydrogenated castor oil does not develop rancidity nearly as readily, however, as untreated castor oil.

The hydrogenated castor oil used in these experiments was practically completely hydrogenated, having an iodine value of practically zero and a melting point of about 86° C. It was a hard, brittle, more or less translucent, glossy substance which could readily be reduced to a powder.

Cold Cream.—Cold cream, although made by a number of different formulas, consists chiefly of liquid oils (such as mineral oil), wax (spermaceti, etc.), emulsifier and water. The usual proportions are wax 12–20%, oil 40–60% and water 20–35% (2). **Unguentum Aquæ Rosæ,** U. S. P., contains 24.5% waxes, 56% oil and 19% water. This, however, is much stiffer than most commercial cold creams.

EXPERIMENTAL.

In order to ascertain the effect of substitution of hydrogenated castor oil for waxes in cosmetics, a series of cold creams was prepared. The basic formula was high in both wax and water so that the substitution would readily be noticed in comparative stiffness and the absorption of water.

Basic Formula.

Wax	20 Gm.
Mineral Oil	50 cc.
Water	30 cc.
Emulsifier, *q. s.*	

The cream was prepared in the conventional manner by melting the wax and mineral oil and incorporating the aqueous solution of the emulsifier previously heated to the same temperature. An electric mixer was used for emulsification and the product then stirred by hand occasionally until it cooled. In the case of hydrogenated castor oil, because of its higher melting point, a higher temperature was necessary.

Borax Creams.—Borax creams were prepared by using one Gm. of borax as an emulsifier. Prepared with white wax, the creams were well emulsified, fairly stiff (stiffer than commercial products). This product (I) was used as a standard for comparison. Creams were prepared substituting hydrogenated castor oil for the wax. It was found that more rapid and prolonged agitation was necessary to effect emulsification. The product was unsatisfactory, having a "grainy" consistency. When first prepared, it was softer than that prepared with white wax (I), but after standing two days was stiffer than this cream.

Creams were prepared using a mixture of equal parts of white wax and hydrogenated castor oil with the following results:

Amount Used.	Stiffness when Prepared.	After Two Days.
20 Gm.	Much stiffer than I	Much stiffer than I
16 Gm.	Stiffer than I	Stiffer than I
12 Gm.	Slightly softer than I	Same as I
8 Gm.	Quite soft	Slightly softer than I
4 Gm.	Thick liquid	Very soft cream

Creams prepared with a mixture of wax and hydrogenated castor oil readily emulsified and did not possess the "grainy" consistency which characterized those prepared with the hydrogenated castor oil alone. All of these creams became stiffer after standing for two days.

Triethanolamine Creams.—Creams were prepared using two cc. of triethanolamine and eight Gm. of stearic acid as the emulsifier, the former being dissolved in the water and the latter

melted with oil and wax. These creams emulsified easier than borax creams, the creams were more jelly-like and translucent, especially when first prepared, and the creams were stiffer (due to the stearic acid content).

Creams were prepared with white wax, spermaceti and hydrogenated castor oil. The first was well emulsified and stiffer than I (made with borax). This (II) was used as a standard for comparison of triethanolamine creams. The cream prepared with spermaceti was satisfactory when first prepared, but after standing two days was yellow colored and water had separated. The hydrogenated castor oil cream emulsified readily and was free from the "grainy" consistency of the borax cream. It was about the same consistency as the wax cream (II) when first prepared, but after standing for two days was much stiffer.

Creams were prepared using equal parts of white wax and hydrogenated castor oil and with equal parts of spermaceti and hydrogenated castor oil. In each case the cream was stiffer than with either base alone. The wax-hydrogenated castor oil cream was softer than the spermaceti-hydrogenated castor oil cream when first prepared, but after two days both creams had stiffened and were about the same consistency. Creams prepared with one part of white wax to three of hydrogenated castor oil and vice versa were softer than those made with equal parts.

Creams were prepared using a mixture of equal parts of white wax and hydrogenated castor oil with the following results:

Amount Used.	Stiffness when Prepared.	After Two Days.
20 Gm.	Much stiffer than II	Much stiffer than II
16 Gm.	Stiffer than II	Stiffer than II
12 Gm.	Slightly softer than II	Same as II
10 Gm.	Softer than II or I	Same as I
4 Gm.	Much softer than I or II	Slightly softer than I

CONCLUSIONS.

1. Hydrogenated castor oil (m. p. 86° C.) is unsatisfactory for a borax cold cream when used alone, but is very satisfactory when triethanolamine stearic acid is used as emulsifier.

2. Creams prepared with hydrogenated castor oil are stiffer than those prepared with white wax or spermaceti.

3. A mixture of equal parts of hydrogenated castor oil with white wax or spermaceti possesses greater hardening power than any of the bases alone.

4. The total solidifier content of cold creams may be reduced by 40% by using a mixture of equal parts of hydrogenated castor oil with wax.

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THE APPLICATION OF STATISTICAL METHODS TO PHARMACEUTICAL RESEARCH. V. HOW MANY ARE ENOUGH?*

BY JAMES C. MUNCH.[1]

"When it is not in our power to determine what is true, we ought to act according to what is most probable" (14). Gauss' Law of Errors states that the probability of an error of observation having a magnitude "x" is $y = h\ e^{-h^2x^2}dx$. The probability integral derived from this law, when "P" represents the probability of occurrence of any particular error (1, 8, 10, 14, 15, 17) is

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* Scientific Section, A. PH. A., New York meeting, August 1937.

[1] John Wyeth & Brother Inc., Philadelphia, Pa.

$$P = \frac{2}{\pi} \int_0^{hx} e^{-h^2x^2} d\,(hx).$$

If P is taken as 0.5, the resultant value is that which the next observation is equally likely to meet or to exceed. If this "Probable Error" (PE) is taken about the Mean, it indicates the distribution of results in a large number of observations: 25 per cent will be expected to exceed Mean plus PE; 25 per cent will lie between Mean plus PE and Mean; 25 per cent between Mean and Mean minus PE; and 25 per cent will be less than Mean minus PE. It is obvious that the next observation is as apt to fall within the range of values of Mean plus or minus PE as to fall without this range.

In studies on statistically large numbers of animals, the scatter of individual observations has been found to approach a normal frequency curve. Solving the probability integral, various chances of occurrence of errors as multiples of PE have been determined (6, 17, 20, 24, 30). The most useful values from these integrations are shown in Table I. The first column shows the quotient obtained by dividing

TABLE I.—ODDS AGAINST OCCURRENCE OF DEVIATIONS.

k.	Odds (to 1).
1.0	1
1.48	2
2.0	5
3.0	21
3.25	35
3.5	50
3.82	100
4.15	200
4.4	333
4.6	520
4.9	1000
5.2	2000
5.5	5000
6.0	19,000
7.0	435,000
7.4	1,750,000
8.0	1,500,000,000

TABLE II.—APPLICATIONS OF FORMULA:

$$N = 2\left(\frac{k \times PE}{Diff.}\right)^2.$$

k.	PE.	$Diff.$	N.
2.0	10	10	8
3.0	10	10	18
3.82	5	5	29
	5	10	7
	10	38	2
	10	10	29
	10	5	117
	10	1	2918
	20	10	116
4.9	10	10	48
	10	5	192
	20	10	192
	20	5	768

any particular deviation by PE, or is a column of multiples of PE. The second column shows the odds against the occurrence of a deviation as great as or greater than this multiple. For example, the odds are 5 to 1 against the occurrence of a deviation greater than 2 PE; 100 to 1 against the deviation 3.82 PE; 1,500,000,000 to 1 against a deviation of 8 PE, etc.

The value $\frac{\text{DEVIATION}}{PE}$ may be designated as "k." The PE of a single observation is the deviation expected when the next single observation is made. PE of the Mean, representing the deviation to be expected if another set of the same number of measurements should be made upon the same material under the same conditions, is obtained by dividing $PE_{sing.}$ by the square root of the number of samples analyzed.

A number of studies have been made to determine the relationship between

dose and effect (2, 3, 4, 5, 6, 7, 9, 12, 13, 16, 18, 19, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30). In certain types of assays, such as toxicity, the "all or none" law may be employed. A lethal dose may be defined as the dose killing all test animals. A sub-lethal dose may be defined as that dose killing a certain percentage of the animals injected. By using a sub-script indicating the number of animals tested, and another sub-script indicating the percentage giving any desired degree of effect ($_nED_{\%}$), this standard curve relationship may be broadened to cover various quantitative bioassays. Many investigators prefer the Median Lethal dose, $_nLD_{50\%}$.

The number of animals required for an assay depends upon three factors: the degree of certainty to be placed in the results ("*k*"); the probable error of the assay (*PE*); and the difference which is considered to be discriminatory ("*Diff.*"). Of the variety of formulas for determining "how many are enough?" that formula suggested by Haynes and Judd (11) and further developed by Denny (6) for calculating the number of fruits required for adequate analytical samples, seems the simplest and most readily understood:

$$N = 2\left(\frac{k \times PE}{Diff.}\right)^2$$

When two of the four variables in this equation are arbitrarily made constant, the third variable will vary as a function of the fourth variable. If three variables are fixed, the expression becomes invariant. To illustrate the application of this formula, a series of examples have been worked out, with the results in Table II.

How many animals will be required for an assay in which the degree of certainty sought is 100:1, *PE* is 10 per cent, and the difference to be detected is 10 per cent? Substituting these values in the equation,

$$N = 2\left(\frac{3.82 \times 10}{10}\right)^2 = 2 \times (3.82)^2 = 29$$

When *PE* and *Diff.* are identical, and cancel out, the equation is simplified to:

$$N = 2\,k^2$$

when *PE* and *Diff.* are not identical, the longer formula must be used.

CONCLUSION.

A formula has been developed to determine the number of animals required to produce a specified degree of assurance that a particular difference in experimental results is statistically significant.

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PHYTOCHEMICAL STUDY. SEED OF THE MAGNOLIA GRANDIFLORA.*

BY ST. ELMO BRADY.[1]

The magnolia tree is one of the most interesting and beautiful of the trees which are embraced in the flora of North America. In the southern part of this country it grows to a magnificent height and is prized highly as an ornamental tree primarily for its beautiful, well-scented white flowers. No complete chemical examination has hitherto been made of the seed of this tree, and the constituents of the fatty oil have been only imperfectly known. Most of the published works have been confined chiefly to the examination of the volatile oil of the leaves and bark. Proctor (1) made an examination of the fruit of the *Magnolia tripetala* and reported the isolation of crystals during the course of several experiments without indicating anything as to their composition. Rawlins (2) examined the leaves of the *Magnolia glauca*, L., and recorded the presence of crystals, calcium oxalate, volatile oil, and extracts which possess a bitter taste, impart fluorescence to chloroform, and after boiling with sulfuric acid reduce Fehling's solution. Randolph (3) made a study of the bark of *Magnolia grandiflora* and recorded the following constituents: tannin, starch, saccharine and coloring matter. Greshoff (4) examined the bark of several species of the magnolia and reported the presence of a bebeerine-like alkaloid.

The present study is the first of a series which is being carried out in this laboratory on the *Magnolia grandiflora*. Interests in the tree grew out of the reported statements that the bark has been used, domestically, in infusion or decoction for the treatment of rheumatism and malaria; and tinctures of the bark in brandy or whisky are said to produce cures in chronic cases of chills and fevers

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when quinine failed. The future study will be made on the bark with the hope of isolating the supposed principle or principles responsible for the reported efficacy of the bark in malaria.

The seeds used in the present study were collected on the campus of the University during the latter part of October, after they had fully matured. A large quantity of the seed was collected and immediately subjected to examination.

EXPERIMENTAL PART.

Preliminary Examination.—Twenty grams of the seed were separated into the skin with the fleshy portion and the inner seed which is covered with a bony-like shell. No effort was made to separate the bony covering from the embryo.

Weight of the whole fresh seed	20.00 Gm.
Weight of skin and fleshy portion	9.87 Gm.
Weight of embryo and covering	10.13 Gm.

The parts of the seed were extracted separately with ether. The color of the ethereal extract of the skin and fleshy portion was a decided orange but on the concentration of the solution the color changed to a red, and the residue was of a beautiful dark red color. After drying to constant weight the residue amounted to 4.5 Gm. or 22.5 per cent of the whole seed. The residue from the ether extract of the embryo and covering was of a yellow-orange color and amounted to 4.2 Gm. or 21 per cent of the whole seed.

The total ether extract, therefore, amounted to 43.5 per cent of the total weight of the seed.

Alcohol was added to each of the residues and allowed to remain over night in the refrigerator. The alcoholic solution of the residue from the skin and fleshy portion of the seed showed the presence of a small amount of crystals which were separated and gave the Liebermann reaction for phytosterol; the solution of the residue of the embryo, however, did not deposit such crystals.

A portion of the ground seed was tested for alkaloids with Prollius' fluid but with negative results.

Another portion of the ground seed was extracted in a Soxhlet apparatus with light petroleum (b. p. 30–50°) which yielded 42.5 per cent of fatty oil.

Ash Content.—The ash content was determined from the whole fresh seed and the following results were obtained.

TABLE I.—ASH DETERMINATION.

	Per Cent.*
Total ash	2.16
Water-soluble ash	0.40
Water-insoluble ash	1.77
Acid-soluble ash	1.66
Acid-insoluble ash	0.113

* Each result represents the average of several determinations.

The whole fresh seed was first boiled with alcohol to remove a wax-like coating. This material introduces difficulties in the study of the ground seed as examination progresses unless removed. After the removal of the alcoholic extract the seed was ground in a mill and extracted with petroleum ether. The extraction was continued until the seed was exhausted. The solvent was removed and the remaining oil heated under reduced pressure to remove the last traces of the solvent. The clear red oil possessed a distinctly pleasant odor recalling that of the magnolia blossom. It colored cotton cloth a deep yellow which was removed only with difficulty. The oil solidified to an orange-colored solid between 5–7°.

Another portion of the ground seed was extracted by continuous percolation with hot alcohol. After the removal of the exhausted seed pulp there separated a heavy oil which was collected. On cooling more of the oil separated. The oil was permitted to stand undisturbed for a week when a small amount of a red solid separated, which was removed by filtration. The solid

was practically insoluble in cold alcohol but dissolved more readily in hot alcohol to an orange solution. This solid will be discussed later.

The residual seed cake from the above extraction with alcohol was further extracted with petroleum ether to remove any residual oil.

EXAMINATION OF ALCOHOL FILTRATE.

The alcohol extract from which the oil separated was concentrated and more oil separated, and was removed. The solvent was finally removed as far as possible and there remained a dark semi-solid residue which was mixed with a little water and subjected to steam distillation. Several liters of the distillate were collected and extracted with ether. The ethereal extract was dried over anhydrous sodium sulfate and the solvent removed. There remained a small amount of oil (1.456 Gm.) with a very pleasant aromatic odor. This was fractionally distilled, giving two fractions. Fraction (1), amounting to 0.8693 Gm., was of a light yellow color with the following physical constants: b. p. 115–120° at 6 mm.; specific gravity, 0.9474 at 25/25°; refractive index, 1.4995/25°. The oil formed no additional product with sodium bisulfite nor did it give a coloration with ferric chloride solution. Fraction (2), amounting to 0.4256 Gm., boiled at 120–135° at 6-mm. pressure with slight decomposition. The refractive index was 1.519 at 25°. It gave a slightly greenish yellow coloration with ferric chloride solution but no additional product with the bisulfite.

There remained a very small amount of a dark viscous residue.

After the steam distillation as described there was left in the distillation flask a dark-colored aqueous liquid which had the odor of burnt sugar and a heavy oily layer. These layers were separated.

THE AQUEOUS LIQUID.

On standing for several weeks there was deposited a quantity of a dark reddish brown solid in the aqueous liquid which was removed by filtration. The aqueous solution was repeatedly extracted with ether, the ethereal liquid washed, dried and the solvent removed. A small amount of a brown, viscous mass remained which was soluble in sodium carbonate but could not be purified sufficiently to obtain a product which could be analyzed.

The aqueous liquid, after extraction with ether, was treated with basic lead acetate which produced a light yellow precipitate. This was filtered, thoroughly washed, suspended in water and decomposed by hydrogen sulfide. The filtrate from the lead-sulfide precipitation was concentrated under diminished pressure but deposited nothing crystalline on standing.

The filtrate from the basic lead-acetate precipitate deposited a light yellow solid on standing which was not further investigated. This solid was removed and the liquid freed of the excess lead with hydrogen sulfide, filtered and concentrated to a heavy reddish brown syrupy liquid which yielded a *d*-phenylglucosazone, melting at 214°. Nothing crystalline could be extracted from this syrupy liquid.

WAX-LIKE SEED COVERING.

The solvent was removed from the alcoholic extract of the whole fresh seed and there remained a semi-solid, yellow material. This was taken up in alcohol and the solution permitted to stand for several hours at room temperature. An oily substance settled out and was removed. The alcoholic solution was placed in the refrigerator over night and only a small amount of a yellow solid separated, which was removed. Water was added to the alcoholic solution just to cause permanent turbidity; and on standing, a large quantity of a white solid separated. Recrystallization of this from alcohol gave white needles, melting at 59°. Further study is being made of this coating material.

EXAMINATION OF THE OIL.

The red oil obtained by extraction with petroleum ether and by percolation with alcohol was filtered and the following physical and chemical constants determined.

The oil was first subjected to steam distillation. The distillate contained no volatile oil and a very slight acid reaction was indicated.

The extracted oil was separated from the water, the latter extracted with ether to remove the suspended oil, and the solvent removed. The remaining oil was added to the main portion

TABLE II.—CONSTANTS OF OIL.

	Extracted Oil.	Neutral Oil.
Specific gravity, 25/25°	0.9652	0.9537
Refractive index at 25°	1.480	1.4702
Iodine number (Hanus)	89.5	95.3
Saponification value	182.5	181.7
Unsaponifiable matter %	2.83	2.17
Saturated acids (corrected) %	20.20	19.18
Unsaturated acids (correction) %	72.63	73.77
Iodine number of unsaturated acids	114.4	.....

and the whole was hydrolyzed in the usual manner by heating with alcoholic potassium-hydroxide solution. The greater part of the alcohol was removed, water added and the solution of the potassium salts was extracted repeatedly with ether. The combined ethereal solutions were washed with water, dried over anhydrous sodium sulfate, and the solvent removed when a small amount of a yellow crystalline solid was obtained. This was fractionally crystallized from ethyl acetate and alcohol and was obtained in colorless needles, melting at 132°.

This substance, when dissolved in chloroform to which a little acetic anhydride had been added and treated with a drop of sulfuric acid, developed a blue coloration, rapidly changing to green, and finally to brown. This substance is evidently a phytosterol.

THE FATTY ACIDS.

The alkaline aqueous solution of the potassium salts, after extraction with ether, was acidified with dilute sulfuric acid and the liberated fatty acids taken up with ether. The ethereal solution was washed with water, dried over anhydrous sodium sulfate and the solvent removed. A determination of the acetyl value of the mixed fatty acids showed a negative result. No volatile acids could be detected either in mixed acids or in the aqueous filtrate from which the acids had been extracted.

The percentages of the saturated and unsaturated acids were determined by the lead-salt ether method (5) and by the method of Twitchell (6) with the following results.

Lead-Salt Ether Method.	Lead-Salt Alcohol Method.
Saturated acids 19.18 per cent	20.20 per cent*
Unsaturated acids 72.25 per cent	72.63 per cent

* The iodine number was small enough to be negligible.

SATURATED ACIDS.

The saturated acids which were separated by the above methods were esterified with absolute alcohol, dry hydrogen chloride being used, and the resulting esters fractionally distilled under diminished pressure. The data for the distillation are given in Table III. The preliminary distillation was made from a 500-cc. Claissen flask, giving two fractions and a residue.

Fraction.	Tempt.	Pressure.	Refractive Index.	Color.	Amounts in Gm.
A	To 170°	4 mm.	1.4380/27°	Sl. yellow	76
B	170–185°	4 mm.	1.4405/27°	Sl. yellow	43
	Residue, dark red solid				1
					120

The final distillation was made from a 125-cc. Claissen flask. The auxiliary neck of the flask was extended by sealing on a modified Vigreux distilling column nine inches in length and this proved very efficient in the distillation. Fractions A and B were distilled under a pressure of less than 1 mm., giving four fractions and a residue and three fractions and a residue, respectively.

The further purification of the various fractions involved fractional crystallization of the esters. Inasmuch as the same procedure was used in each case, the process will be described in some detail. Fraction (1) (b. p. 145°) was dissolved in absolute alcohol in which it is very soluble and the solution placed in the refrigerator at a temperature of 0° to 5° over night. Beautiful white

TABLE III.—FRACTIONAL DISTILLATION OF ESTERS.

Fraction A (b. p. −170°/4 mm.).

Fraction.	Tempt.	Pressure.	Refractive Index.	Color.	Amount in Gm.
1	To 145°	>1 mm.	1.4380/25°	Colorless	28.0
2	145–155°	>1 mm.	1.4385/25°	Colorless	14.0
3	155–160°	>1 mm.	1.4395/25°	Colorless	7.5
4	160–165°	>1 mm.	1.4400/25°	Colorless	23.0
	Residue, solid				1.5
					74.0

Fraction B (b. p. 170–185° /4 mm.).

1	To 160°	>1 mm.	1.4385/25°	Colorless	20
2	160–165°	>1 mm.	1.4412/25°	Colorless	11
3	165–170°	>1 mm.	1.4420/25°	Colorless	10
	Residue, solid				1
					42

needles separated which were filtered without removing the flask from the refrigerator. Care was taken to remove the alcohol as far as possible by suction. The crystals were removed to a glass evaporating dish and allowed to melt. The melted crystals were placed in a vacuum desiccator and the last traces of the alcohol removed. These crystals melted at 25–25.5°, and the melted crystals had a refractive index of 1.4385 at 25°.

The melted crystals were again dissolved in absolute alcohol and submitted to the above procedure. The crystals obtained were long slender needles which melted at 25.5°, the whole thermometer in the bath, and the melted crystals showed a refractive index of 1.4385 at 25°.

Seventeen grams of the crystallized ester were dissolved in a little alcohol and saponified in the usual manner. The potassium salt was obtained in long, flat glistening needles arranged in mats. The free acid crystallized in white, fan-shaped crystals, melting at 62°. Recrystallization from alcohol gave glistening white plates, while from acetone glistening, almost transparent plates were obtained. In each case the melting point was 63°.

The silver salt of the acid was prepared and analyzed.

0.0732 Gm. of salt gave on ignition 0.022 Gm. Ag.
Ag = 30.05 per cent.
0.0733 Gm. of salt gave on ignition 0.0216 Gm. Ag.
Ag = 29.46 per cent.
$C_{16}H_{31}O_2AG$ requires Ag = 29.7 per cent.

The crystals were thus identified as palmitic acid.

Recrystallization of products obtained from the above alcoholic filtrates did not show any substance with a different melting point.

Fraction 2 (b. p. 145–155°) gave white crystals by the above procedure, melting at 25°. The ester on saponification yielded an acid which, after recrystallization from alcohol and acetone had a melting point of 63°. This acid was analyzed and identified as palmitic acid.

Fraction 3 (b. p. 155–160°) showed the presence of palmitic acid.

Fraction 4 (b. p. 160–165°). The colorless fraction was dissolved in absolute alcohol and crystallized by the above procedure. The crystals showed a melting point 18–21°. These were converted into the acids and fractionally crystallized when the following fractions were obtained: Fractions, (*a*) m. p. 62°; (*b*) m. p. 62°; (*c*) m. p. 60°; (*d*) m. p. 59.5°; (*e*) m. p. 59–59.5°; (*f*) m. p. 59°.

It is obvious that the first three fractions are palmitic acid while the fractions, *d*, *e*, *f*, represent a mixture of palmitic acid and a small amount of a lower melting acid.

The filtrate from the final crystallization was diluted with water and the precipitated acid collected and dried. The melting point was 56°. Recrystallization from acetone, methyl and ethyl alcohols did not materially alter the melting point.

The silver salt of this acid was prepared and analyzed.

0.0985 Gm. of salt gave on ignition 0.0315 Gm. Ag.
Ag = 31.99 per cent.
0.0705 Gm. of salt gave on ignition 0.0225 Gm. Ag.
Ag = 31.90 per cent.
$C_{14}H_{28}Ag$ requires Ag = 32.2 per cent.

The acid was thus identified as myristic acid.

Fraction B (B. P. 170–185).—The various fractions obtained by a more careful separation of this fraction were subjected to the same procedure as indicated. Fraction 1 (b. p. to 160°) was primarily palmitic acid; fraction 2 (b. p. 160–165°), a mixture of palmitic and myristic acids.

Fraction 3 (B. P. 165–170°).—The pure ester melted at 22.5°. The acid obtained by saponification of the ester had a melting point of 64.66°. On dissolving the acid and in cold alcohol a portion did not go into solution very readily and was filtered off and called the "insoluble portion." Recrystallization of this "insoluble portion" gave a product melting at 68°; while the acid obtained from the soluble ester melted at 62°.

The silver salt of the acid melted at 68°, was prepared and analyzed.

0.125 Gm. of salt gave on ignition 0.0343 Gm. Ag.
Ag = 27.44 per cent.
0.096 Gm. of salt gave on ignition 0.0263 Gm. Ag.
Ag = 27.39 per cent.
$C_{18}H_{35}O_2Ag$ requires Ag = 27.55 per cent.

The acid was thus identified as stearic acid.

The solid residues were mixed and treated with cold alcohol and a portion of it was more soluble than another. The sparingly soluble portion was removed and recrystallized. The ester had a melting point of 49.5°. The acid obtained by the hydrolysis of the ester, after recrystallization from dilute alcohol, melted at 76–77°.

The silver salt of this acid was prepared and analyzed.

0.0932 Gm. of salt gave on ignition 0.0238 Gm. Ag.
Ag = 25.53 per cent.
0.0754 Gm. of salt gave on ignition 0.0192 Gm. Ag.
Ag = 25.46 per cent.
$C_{20}H_{39}O_2Ag$ requires Ag = 25.67 per cent.

The acid was thus identified as arachidic acid.

SEPARATION AND IDENTIFICATION OF UNSATURATED ACIDS.

Oxidation of the Unsaturated Acids.—Thirty grams of the mixed acids were oxidized with dilute alkaline permanganate solution according to the method of Hazura and Grüssner as given by Lewkowitsch (7), and the oxidation products separated into two fractions: (*a*) 5.06 Gm. representing sativic acid having a melting point of 169.5° which, after recrystallization, melted at 172.5°. The acid value was found to be 162.9 as compared with the theoretical value of 161.2. (*b*) 7.56 Gm. from the ether after evaporation was fractionally crystallized and two acids were obtained in a pure form, (1) melting at 121°, and (2) melting at 130°. Both were dihydroxystearic acids with acid values of 178.9 and 179.0, respectively, compared with the theoretical value of 180.5. The presence of sativic acid indicates linoleic acid. The two dihydroxystearic acids indicate the presence of oleic acid. The isolation of the two oxidation products of oleic acid with different melting points leads one to assume the presence of isomeric oleic acids in the mixture.

Preparation of the Bromine Addition Products.—Twenty-five grams of the unsaturated acids were dissolved in dry ether, 200 cc., and 20 cc. of glacial acetic acid added. The ethereal solution was cooled to −5° and bromine slowly added, maintaining the temperature between −5° and 0° throughout the addition. When a permanent bromine color had been attained the whole was set aside in the refrigerator over night. No separation of solid material was noticed indicating the absence of linolenic acid. The bromination products soluble in ether were freed from the excess bromine by treatment with sodium thiosulfate, the ethereal solution washed, dried over anhy-

drous sodium sulfate, the ether removed and the residue refluxed with petroleum ether and the whole permitted to stand over night in the refrigerator. The tetrabromide of linoleic acid separated in wart-like crystals which, after washing with petroleum ether and drying, melted at 114°. Analysis of the bromide gave the following results.

0.4253 Gm. bromide gave 0.5320 Gm. AgBr.
Br = 53.20 per cent.
0.4020 Gm. bromide gave 0.5026 Gm. AgBr.
Br = 53.18 per cent.
$C_{18}H_{32}O_2Br_4$ requires Br = 53.33 per cent.

Thus indicating the presence of linoleic acid.

The filtrate was concentrated and permitted to stand for several hours but no further precipitation of the bromide took place. The solvent was completely removed, the last traces in the vacuum. This fraction should contain the oleic dibromides and the soluble tetrabromides of linoleic acid. After standing for a week some more of the solid separated, which was filtered, washed well with petroleum ether, and dried in the desiccator. These crystals melted at 114°.

The residual liquid bromide was analyzed for bromine.

1.755 Gm. bromide gave 1.553 Gm. AgBr.
Br = 37.16 per cent.
2.264 Gm. bromide gave 1.971 Gm. AgBr.
Br = 37.04 per cent.
$C_{18}H_{34}O_2Br_2$ requires Br = 36.18 per cent.

Thus oleic acid is identified.

The analyses of the bromine addition products of the unsaturated acids together with the oxidation products of these acids confirm the presence of oleic and linoleic acids. The analytical results of the residual liquid bromide show the product to be almost pure oleic dibromide.

In another experiment, after the concentration of the liquid bromides under reduced pressure, a bromide separated which melted at 56°. Recrystallization from petroleum ether resulted in white needles, melting at 57–58.5°. This amounted to one Gm. Unfortunately after several attempts with other portions of the liquid bromides no more of the low melting isomer could be isolated.

TABLE IV.—ANALYSIS OF UNSATURATED ACIDS.

Weight of unsaturated acids	25.00 Gm.	
Weight of linoleic tetrabromide (m. p. 114°)	7.54 Gm.	
Weight of linoleic tetrabromide (m. p. 57–58.5°)	1.00 Gm.	
Weight of liquid bromide	30.10 Gm.	
Bromine in tetrabromide %	53.20	53.18
Bromine in liquid bromide %	37.16	37.04

REGENERATION OF THE UNSATURATED ACIDS FROM THEIR RESPECTIVE BROMIDES.

The procedure of Rollett (8) was used in the preparation of the unsaturated acids from their bromides. Fifty grams of the liquid bromide were dissolved in methyl alcohol, 50 Gm. of zinc added and methyl alcoholic hydrogen chloride (150 cc. of 11%) was dropped into the refluxing solution. After all of the alcoholic hydrogen chloride had been added the whole was refluxed for several hours. The solvent was removed and the ester was saponified in the cold by dissolving in 5 per cent potassium hydroxide and allowing to stand over night. The acid obtained was purified and had an iodine value of 91, theoretical value for oleic acid is given as 90.07.

The same procedure was used in the case of the tetrabromide of linoleic acid. The free acid was distilled and the pure fraction boiled at 225° at 12-mm. pressure. Two samples showed iodine values of 178.6 and 179.1, respectively. The theoretical value for linoleic acid is 181.42.

Thus the presence of the oleic and linoleic acids were established by the analysis of the oxidation products of the mixed unsaturated acids, the preparation and analysis of the respective bromides, and finally, from the iodine values of the regenerated acids.

OXIDATION OF THE NEUTRAL FAT.

A study of the oxidation products of the neutral fat was made. For this purpose 310 Gm. of the fat were boiled under a reflux with aqueous sodium carbonate. The mixture was allowed to separate and cool. The oil was removed and dried. No examination was made of the brownish colored aqueous layer at this time.

The neutral oil was filtered to remove any sediment and dissolved in ether so that the solution represented approximately a 25 per cent one. Two volumes of warm acetone were added and the beautiful cherry-red solution was placed in the cold room for twenty-four hours. During this time a light yellow, soft material was deposited. This was removed by the aid of the pump. The solvent was removed from the oil and the last traces under reduced pressure. The oil remaining was of a dark red color. This process was repeated until no more of the solid separated. This solid, after purification, crystallized in needles melting at 62°. Further study is being made on this product.

The physical and chemical constants of this purified oil are given in Table II.

Two hundred grams of the neutral purified oil were dissolved in 2000 cc. of dry acetone and boiled gently on the water-bath. Two hundred grams of powdered potassium permanganate were added in small quantities and the mixture refluxed for four hours. The addition of the permanganate must be done cautiously as the reaction can become violently reactive. After this time the acetone was removed as far as possible and the residue thoroughly mixed with about 200 Gm. of sodium bisulfite and poured into 1000 cc. of water. This solution was boiled and dilute sulfuric acid added until the solution was free of manganese dioxide. On cooling the solution was extracted several times with ether. The ethereal extracts were combined, washed with water, dried and the solvent removed. The residue was taken up in hot water and dilute sodium carbonate solution added until it was alkaline to litmus. The aqueous solution was extracted with ether to remove any unchanged oil and neutral substances.

THE AQUEOUS PORTION.

The aqueous layer was made acid with dilute sulfuric acid and extracted with ether. After the removal of the solvent a residue remained, consisting of a solid and heavy liquid. The mixture was separated and the solid washed with petroleum ether. This ether was added to the liquid part of the extract.

The white solid was recrystallized from alcohol several times and finally crystals were obtained which had the constant melting point of 106–107°. The acid was identified as azelaic acid which melts at 106.5°.

A second acid was obtained from this crystallization which had the melting point 56–57°.

The liquid acid fraction was soluble in petroleum ether and the solution was filtered to remove some sediment. After the removal of the solvent the remaining oily liquid was fractionated at atmospheric pressure with the following results:

Fraction.	Temperature.
1	To 90°
2	90–120°
3	120–205°
4	205–230°
5	230–240°
6	240–255°
7	Solid residue

Fractions (1) and (2) represent in the main the solvent and acetic acid; fraction (3), lower acid with a mean equivalent of 123.2. Fractions (4), (5) and (6) were mixed and refractionated and finally a product was obtained which boiled at 250−255° and represented the greater portion of the material used.

Further purification of the fraction consisted in its conversion into the barium salt which is sparingly soluble in hot alcohol and practically insoluble in cold alcohol. On dissolving the salt in a large volume of boiling alcohol and allowing to cool the characteristic silky needles of the barium salt separated. These were removed and after drying, analyzed.

0.2323 Gm. salt gave 0.120 Gm. $BaSO_4$.
Ba = 30.37 per cent
$Ba(C_9H_{12}O_2)_2$ requires Ba = 30.45 per cent.

The acid is thus identified as nonanoic acid.
The residue was identified as azelaic acid.

UNSAPONIFIABLE MATTER.

The unsaponifiable matter was obtained by extracting the aqueous solution of the potassium salts from the hydrolysis of the oil with ether. After drying the ethereal solution over anhydrous sodium sulfate and removing the ether, a red solid material remained. A chemical study of this is in progress. The work done so far would indicate that there are at least two phytosterols, an oil and coloring matter.

COLORING MATTER.

Mention has already been made of the separation of a dark red solid material from the oil which had been standing for a week. This colored solid was placed in a desiccator and after some time it was bleached out. This solid was practically insoluble in the usual organic solvents after bleaching. A small portion was burned on a platinum foil and a residue remained which was insoluble in water but readily soluble in hydrochloric acid. This solution gave a decided test for magnesium. It is not known at this time whether the magnesium is a definite part of the color molecule or simply an admixture. At various times during the preparation and analysis of the oil a gray solid would separate at the point in the procedure where the unsaponifiable matter was extracted from the aqueous solution of the potassium salts. This gray solid collected between the aqueous and ether layer. Several tests have been made with this material. Refluxing with alcoholic potassium hydroxide and with concentrated hydrochloric acid apparently caused no change. It gave the test for magnesium.

In the examination of the unsaponifiable matter a small amount of red coloring matter was isolated which was very intimately associated with another pigment which was of an orange color. It is unusually difficult to separate the two pigments from the oil. All are exceedingly soluble in carbon disulfide and the resulting solution is blood red. A large volume of absolute alcohol was added to the carbon disulfide solution and the whole allowed to stand over night in the refrigerator. A dark red solid separated which was removed by the aid of suction. The process of purification was repeated and the final product melted at 158–164° which indicated the presence of other substances, possibly oil which is removed with difficulty. The red solid showed all the solubility reactions of lycopin. Solutions in hot ether, alcohol, chloroform and benzene were yellow while in carbon disulfide a blood-red solution was obtained which persisted even in dilute solutions. It bleached to a white solid in the desiccator over phosphorus pentoxide.

Attempts were made to determine the absorption spectra but seemingly there was just sufficient of the orange pigments present to show an almost continuous absorption spectrum. This is to be expected in the case of a mixture because of the relative positions of the absorption bands of carotin and lycopin.

The refractive index of the isolated red pigment was determined in carbon disulfide solution and was found to be 1.603 at 25°, Kohl (9) gives 1.628 for the pure substance. The combustion analysis of this substance was far from satisfactory.

The alcohol-carbon disulfide filtrates were combined and concentrated. After standing over night in the refrigerator a mixture of red oil and an orange-yellow solid separated. This solid was removed and dissolved in absolute alcohol to a yellow solution. Very little oil separated with the orange-yellow solid after standing over night. It was impossible, under the conditions, to remove the last traces of oil from the pigment because of the small quantity of the material at our command. This orange-yellow pigment, like the red, bleached when exposed to the air.

The blood-red oil remaining was of a more limpid nature than the original oil and showed some differences in properties. For comparison the specific gravity and refractive index of the original oil and this oil are indicated.

	Original Oil.	Final Oil.
Specific gravity	0.9652 25/25°	0.9456 25/25°
Refractive index	1.480/25°	1.4950/25°

There is little doubt that the red color of this oil is due to the presence of the pigment.

A critical study of the pigments of the magnolia seed is now in progress together with that of the whole unsaponifiable matter.

SUMMARY.

The material employed for this investigation consisted of the whole fresh seed of the *Magnolia grandiflora* which was collected on the campus of the University during the month of October.

The seed was subjected to preliminary tests and gave no evidence of alkaloid or glucoside.

The ash content of the fresh seed was determined and gave the following results: Total ash, 2.16 per cent; water-soluble ash, 0.40 per cent; water-insoluble ash, 1.77 per cent; acid-soluble ash, 1.66 per cent; and acid-insoluble ash, 0.113 per cent. In view of the high acid solubility it is desirable to make a complete analysis of the ash which is in progress.

An alcoholic extract of the ground seed, when distilled with a current of steam, yielded a small amount of a light yellow volatile oil with a very pleasant aromatic odor. The oil was fractionated, giving two fractions: (*a*) light yellow oil, very pleasant odor, and boiling at 115–120° at 6-mm. pressure. It had a specific gravity of 0.9474 at 25/25°; index of refraction 1.4995/25°. It formed no addition product with sodium bisulfite nor did it give any coloration with ferric chloride solution. (*b*) This fraction was darker in color but possessed an odor similar to the other fraction. It boiled at 120–135° at 6-mm. pressure with slight decomposition. The refractive index was 1.519/25°. It gave a slightly greenish yellow coloration with ferric chloride solution but no addition product with the bisulfite.

The portion of the extract which was soluble in water contained a sugar which yielded a *d*-phenylglucosazone, melting at 214°, some tannin but nothing crystalline. A quantity of reddish brown solid separated from the aqueous solution on standing, which needs further investigation.

The fatty oil of the entire seed when ground and extracted with petroleum ether amounted to 42.5 per cent. This oil showed the following constants: Specific gravity, 0.9652 at 25/25°; refractive index, 1.428 at 25°; iodine number (Hanus), 89.5; saponification value, 182.5. The composition of the oil was as follows: Saturated acids, 20.20 per cent; unsaturated acids, 72.63 per cent; unsaponifiable matter, 2.83 per cent. The saturated acids resolved themselves into myristic, palmitic, stearic and arachidic acids; while the unsaturated acids were, isomeric, oleic and linoleic acids. Of the saturated acids palmitic acid predominated, the others in small quantities totaling probably less than 5 per cent. Oleic acid predominated in the mixture of unsaturated acids.

Oxidation of the oil in alkaline permanganate solution gave sativic and two dihydroxystearic acids; oxidation in boiling acetone with permanganate yielded acetic and some other lower acids, nonanoic and azelaic acids.

Evidence was obtained of the presence of at least two different pigments belonging, no doubt, to the carotinoid group from their color reactions and bleaching properties. The presence of phytosterol was indicated.

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ESTIMATION OF IODIDES IN COMPLEX MIXTURES.*

BY J. B. FULLERTON, W. J. WATKINS AND C. L. GRAHAM.

The estimation of inorganic iodine in complex mixtures has frequently been a source of difficulty. There have been numerous methods in the literature for the determination of iodine in ferrous iodide pills; but there will be no attempt made to list the papers describing the various methods. None of the methods recommended were successful in this laboratory, and it is assumed they were not generally satisfactory, else we would not find references to so many attempts on the problem.

Scott (1) gives a method for the decomposition of an iodide with nitrous acid and the subsequent extraction of the free iodine by means of carbon disulfide. The solution of iodine is then titrated with standard thiosulfate. In the same connection there is also given a method for liberation of iodine by the addition of hydrogen peroxide to a solution acidified with phosphoric acid. The liberated iodine is then distilled into a solution of potassium iodide and titrated with thiosulfate.

Working on a modification of Scott's method we have arrived at the following procedure:

Weigh enough of the finely powdered material to represent approximately 5 grains of potassium iodide (or an equivalent amount of iodine), and transfer to a separatory funnel. Add 50 cc. of water and, if alkaline, neutralize with phosphoric acid, finally adding 5 cc. in excess. Add 25 cc. of hydrogen peroxide and agitate thoroughly. Allow to stand a few minutes to be sure the reaction is complete and extract the liberated iodine with several portions of chloroform until the iodine has been removed, as can be told from the color. Collect the chloroform extractions in an iodine flask containing about 4 Gm. of potassium iodide in 25 cc. of water. Titrate with $N/10$ thiosulfate solution using starch as indicator.

The reaction between hydrogen peroxide and iodide in an acid solution is expressed by the following equation:

$$H_2O_2 + 2I^- + 2H \rightleftharpoons 2H_2O + I_2$$

We have found this method to be rapid, accurate and capable of a wide variety of uses. As previously stated, it was originally devised for the determination of iodine in ferrous iodide pills and has since been used for the estimation of iodine in various complex pill and tablet mixtures. It is satisfactory for mixtures of iodides with drug extracts, ferrous salts, reduced iron or arsenic. Obviously the same method could be used for the separation of iodine from the other halogens; but for simple mixtures of such, it is not as convenient as the well-known method of titration with KIO_3.

* From the Control Laboratory of the Upjohn Co., Kalamazoo.

An idea of the results to be expected by using this method on various mixtures may be obtained from the following tables.

Table I shows comparative results using the U. S. P. titration and the proposed method, with potassium iodide alone.

TABLE I.—POTASSIUM IODIDE ALONE.

		U. S. P. Titration.		Proposed Method.	
KI	0.35 Gm.	0.3490 Gm.	99.71%	0.3496 Gm.	99.99%
		0.3486 Gm.	99.60%	0.3498 Gm.	99.99%

Table II gives the results obtained in mixtures of potassium iodide with sodium chloride and sodium bromide: (*a*) the three salts are in equal proportions, (*b*) sodium chloride and sodium bromide are each present in twice the quantity of the potassium iodide and (*c*) the sodium chloride and sodium bromide are present in one-half the quantity of the potassium iodide.

TABLE II.—POTASSIUM IODIDE WITH OTHER HALIDES.

(*a*) Mixture Contains:		Potassium Iodide Recovered.	
KI	0.35 Gm	0.3510 Gm.	100.28%
NaCl	0.35 Gm.	0.3505 Gm.	100.10%
NaBr	0.35 Gm.	0.3517 Gm.	100.50%
(*b*) Mixture Contains:		Potassium Iodide Recovered.	
KI	0.35 Gm.	0.3470 Gm.	99.14%
NaCl	0.70 Gm.	0.3465 Gm.	99.00%
NaBr	0.70 Gm.	0.3475 Gm.	99.28%
(*c*) Mixture Contains:		Potassium Iodide Recovered.	
KI	0.35 Gm.	0.3510 Gm.	100.28%
NaCl	0.17 Gm.	0.3505 Gm.	100.10%
NaBr	0.17 Gm.	0.3508 Gm.	100.20%

Table III gives comparative results on syrup of hydriodic acid, using the U. S. P. method and the proposed method.

TABLE III.—SYRUP OF HYDRIODIC ACID.

		U. S. P. Method.	Proposed Method.
Hydriodic acid per 100 cc.	(*a*)	1.397 Gm.	1.389 Gm.
	(*b*)	1.393 Gm.	1.387 Gm.
	(*c*)	1.384 Gm.	1.388 Gm.

Tables IV, V, VI and VII give the results obtained for the analysis of known amounts of iodides in mixtures frequently encountered in pill and tablet assays.

TABLE IV.

		KI Recovered.	
KI	0.25 Gm.	0.2502 Gm.	100.1%
Ferrous sulfate	0.65 Gm.	0.2510 Gm.	100.4%
Sugar	0.15 Gm.	....	....

TABLE V.

		Iodine Theory.	Iodine Recovered.	
Potassium iodide	0.30 Gm.	0.2405 Gm.	0.2381 Gm.	99.00%
Mercuric iodide	0.02 Gm.	....	0.2400 Gm.	99.79%
Ext. echinacea	0.60 Gm.	....	0.2360 Gm.	98.12%
Ferrous carbonate	5.00 Gm.	....	0.2420 Gm.	100.60%

TABLE VI.

		Iodine Theory.	Iodine Recovered.	
Potassium iodide	0.30 Gm.	0.2330 Gm.	0.2280 Gm.	97.8%
Mercuric chloride	0.002 Gm.	....	0.2306 Gm.	99.0%
Mercuric iodide	0.0026 Gm.	....	0.2295 Gm.	98.5%
Arsenic iodide	0.0026 Gm.	....	0.2350 Gm.	100.8%
Ferrous carbonate	0.090 Gm.	....	....	....
Ext. nux vomica	0.002 Gm.	....	....	....

TABLE VII.

		Iodine Theory.	Iodine Recovered.	
Potassium iodide	0.30 Gm.	0.2310 Gm.	0.2331 Gm.	100.90%
Mercuric iodide	0.003 Gm.	....	0.2300 Gm.	99.56%
Hyoscyamus			0.2320 Gm.	100.40%
	0.02 Gm.	....	0.2280 Gm.	98.70%

We have also used a modification of this method for the determination of total iodine in Iodine Ointment as follows:

Place in a separatory funnel about 4 or 5 Gm. of the ointment accurately weighed, and dissolve in about 50 cc. of ether with vigorous shaking. Add an excess of $N/10$ sodium thiosulfate solution, about 30 cc., and mix well. Transfer the aqueous portion to a 250-cc. separatory funnel and extract the ether solution with three more 25-cc. portions of water. Combine all the aqueous washings in the 250-cc. separatory funnel, adding 5 cc. of phosphoric acid and 25 cc. of hydrogen peroxide. Extract the liberated iodine with chloroform and complete the determination as outlined previously.

Table VIII gives comparative results for total iodine in Iodine Ointment as determined by the U. S. P. XI method and by the proposed method.

TABLE VIII.

Ointment.		U. S. P. XI Method.	Proposed Method.
No. 1	Total iodine	6.85%	6.83%
		6.81%	6.89%
No. 2	.....	6.80%	6.85%
		6.90%	
No. 3	.....	6.70%	6.81%
		6.77%	6.65%

SUMMARY AND CONCLUSIONS.

The method outlined has been developed for the determination of iodides in complex mixtures often encountered in control work on tablets and pills. It has also been found satisfactory for total iodine in Iodine Ointment U. S. P.

As yet we have not found any mixture containing an inorganic iodide in which the iodine could not be determined according to this method.

REFERENCE.

(1) Standard Methods of Chemical Analysis, 4th Edition, Vol. 1.

"A PROFESSIONAL DISPENSING PROBLEM."*

BY W. D. STROTHER.[1]

It has been the writer's responsibility for several years to teach a course in "The Art of Compounding." A major part of this course is devoted to the study and discussion of the so-called incompatible prescription. Many of these prescriptions require special methods in filling, and, in many other instances, changes in quantities or ingredients, or both, are essential before dispensing would be permissible.

The usual texts and reference works on this subject have been consulted and each contains hundreds of combinations presenting difficulties in compounding, and some of them would be dangerous or even fatal if dispensed as written. Of course, it is our business to guard and protect the patient against these errors in prescribing. This is a grave responsibility the pharmacist has assumed. It is an important part of a student's training, and must be emphasized again and again.

From the time the course opens until the last day before final examinations the question is frequently asked: "What would you do in this case?" Students are referred to the discussions given in our leading textbooks and articles in the journals relative to this subject, and to a copy of the "Code of Ethics," as approved by the AMERICAN PHARMACEUTICAL ASSOCIATION. About all we can do to answer these questions is to point to the opinions of experts and give them the benefit of our personal experiences. It all seems quite clear, clean cut and precise, and looks fine in a nicely bound book, but somehow when we get out of the class room and a patient brings a prescription to us with an overdose or a badly incompatible mixture, the rules we learned do not seem to apply to our entire satisfaction. Of course we must call the doctor in regard to overdoses. That, as a rule, is not a difficult matter to handle. But what about the use of other non-active ingredients, or minor substitutions, that would correct an otherwise possible dangerous combination? We must, of course, secure the approval of the physician before any changes are made. That we have been taught from the very beginning of our pharmacy training, and should continue to emphasize the importance of carrying out the intentions of the physician in compounding his prescriptions.

Several druggists have been consulted in regard to this phase of dispensing. The majority of them are frank to admit that they have tried discussing such matters with the physician, but were never quite satisfied with the results. The inability of the doctor and the pharmacist to get together on this problem has resulted in an inferior type of service to the patient. Every dispensing pharmacist in America has probably sent prescriptions out that could easily have been improved upon with minor changes, and that did not represent their idea of professional dispensing. The pharmacist has learned, however, that repeated calls suggesting such changes lead to the loss of that physician's business. This the pharmacist cannot afford. Thus we have a condition in which the pharmacist is afraid to suggest or make improvements; the doctor, not knowing he is mak-

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* Presented before the Section on Practical Pharmacy and Dispensing, A. PH. A., New York meeting, 1937.

[1] Associate Professor of Pharmacy, University of South Carolina.

ing errors in prescribing, continues to err, and the patient suffers whatever the ill effects may be.

At this point in compounding that badly written prescription, we should begin to think of the patient, and the first paragraph of the adopted Code of Ethics might be called to mind, which states: "Pharmacy has for its primary object the service which it can render to the public in safeguarding the handling, sale, compounding and dispensing of medical substances."

We try to instil in the minds of our young pharmacy graduates that pharmacy is an "Old and honorable profession." We try to instil in them the necessity of upholding the ethics of the profession. But somehow when he tries to uphold these ethics, he finds that a part of a legitimate business begins to slip away. He learns from experience that it does not pay financially to attempt to render the highest type of service to the patient when that service involves calling the physician.

We believe the doctor wants his patients to have the best possible service. We know the ethical pharmacist wants to coöperate, but, due to a gap in the relationship between the doctor and the pharmacist, it does not seem possible for them to get together and solve this problem. One reason, and probably the chief reason, for this is that the doctor is not keenly aware that such a problem exists and, due to keen competition, the pharmacist is afraid to bring such matters to his attention. We probably will all agree that, if the physician knew he was making errors, he would do all he could to correct them; but he does not know, and if he did, he has not had ample training in compounding to make corrections in all cases. The pharmacist is in a better position to solve this technical problem. The physician will undoubtedly concede us this point. Why, then, does the physician object to the criticism of his prescriptions? The answer might well be, that all pharmacists do not have sufficient knowledge to wisely advise the physician, and further they may not have those indispensable qualities, personality and tact, so necessary to discuss such matters.

Now suppose we had some way of conveying our ideas about ethical compounding to the medical profession in an undistorted manner, by some one outstanding enough to command the respect of the profession; by some one who could make them conscious of the problem, and by some one who could convince them of the financial advantage of correct prescribing, what would be their reaction? Certainly they would support any reasonable scheme that would improve both professions.

With the advent of our four-year course in pharmacy, the registered young pharmacist must have a better knowledge of chemistry and pharmacy than his older brothers, who only spent two years in college, or, perhaps, offered practical experience entirely as a prerequisite to taking the Board examination. The young pharmacist must then have a better appreciation of incompatibilities and the chemical changes that might take place in compounding. Assuming this is true, we should be in a position to-day to render a higher service to both the patient and the medical profession than ever before. Unfortunately, however, we seem to be unable to apply this improved training in a manner acceptable to our higher appreciation of professional pharmacy, for reasons already discussed.

Our graduates are encouraged by their employers to refrain from ever making the slightest change in a prescription. The young graduate soon begins to lose sight of the stress placed on this subject when in college. He begins to feel the

whole subject of incompatibilities is a theory that cannot be applied. Naturally a subject that is not used is soon forgotten. This point was very forcibly brought to our attention within recent weeks. A young honor graduate from a recognized four-year school reported that in filling some seven thousand prescriptions he could only recall one that was of such nature that he considered it necessary to call the physician. A survey had previously been made of his files, noting the prescriptions of one doctor for one year. Five different prescriptions were found that had been written a total of seventy-five times, containing incompatible chemicals that should have been referred to the physician for alterations. This did not include the refills.

One of the factors that has brought this condition about is the pharmacist's attempt to cultivate the friendship of the doctor, thereby securing his prescription business. While the friendship and the professional respect must be cultivated, the results of the present system are not satisfactory. This system has existed for a long time and no immediate signs of reform are in sight. Perhaps our improved educational standards have not been in effect long enough yet to realize the results we hope to obtain. Improved educational requirements will not directly solve this dispensing problem. Some encouraging signs that may eventually bring pharmacy up to a plane it rightfully deserves are, however, beginning to appear. These encouraging signs are in the nature of improved legislation in the several states, eliminating some of the cut-throat devices in competition. If this can be curbed, together with our improved educational status, pharmacists will organize and become more of a fraternal group than has ever existed before.

When this has been accomplished, and not before, the pharmacist may in a large measure correct one of the evils of his profession. As an example of one thing that might be done by organization that could not be done otherwise, incompatible prescriptions that need alteration could be referred to some outstanding pharmacist. His office might assume the title of "Bureau of Professional Dispensing Information." This office would criticize the prescriptions of any given physician, suggest improvements from a chemical and physical standpoint and return the copies and the criticisms to the physician. This office might also be delegated to offer its service in an advisory capacity to the physician, who might be interested in eliminating future incompatible prescriptions.

With some such system, the young pharmacist would be alert and on the watch for an opportunity to display his professional knowledge. There might be a tendency to go to the opposite extreme, but there would always be the intermediary pharmacist to check the overzealous and enthusiastic prescription clerk. The physician would soon learn to take advantage of this super prescription service and the patients would begin to experience a new era in their professional service.

OLIVER KAMM NAMED OFFICIAL OF RESEARCH INSTITUTE.

Oliver Kamm, scientific director of Parke, Davis & Co., has been named a member of the executive committee of the newly formed Industrial Research Institute.

Scientific research men from many fields of industry are represented in the Institute, which was formed to discuss common problems relating to laboratory organization and administration.

MEDICAL REQUIREMENTS OF THE HOSPITAL PHARMACY.*

BY W. J. STAINSBY,[1] M.D.

Before presenting my opinions concerning the *medical* requirements of a hospital pharmacy, it is important that we have a clear understanding of the function of hospitals. It is generally recognized that a hospital has *four* primary purposes:

1. The diagnosis of disease.
2. The treatment of the patient.
3. The teaching of doctors, nurses and medical students.
4. Research.

As regards the diagnosis of disease, the clinician and the diagnostic laboratories are alone concerned, but as regards the other three functions of the hospital, the pharmacy often plays an important rôle. It is my plan to discuss the relationship of the pharmacy to these three important purposes of the hospital.

As regards the first of these, namely, the treatment of the patient, the pharmacy has a distinctly important rôle to play. Therapeutic results depend in large measure upon the pharmacy's dispensing exactly what is ordered. The physician is concerned principally with the question of purity and potency of the drug or biological preparation he is administering. Many pharmacists assume that the information concerning purity and potency as provided by the manufacturer is correct. Experience has shown us that such information cannot always be relied upon either because of lack of care in the manufacturing process or from deterioration following the manufacture of the preparation. The hospital pharmacist should therefore, in the interest of patients, have the necessary training to test the purity and potency of the various drugs he dispenses. If he is able to make these tests, he may at the same time save his institution a considerable amount of money as he will be able to purchase his drugs from smaller, less well-advertised firms often at an appreciable reduction in price. As soon as pharmaceutical firms realize that a hospital pharmacy makes a practice of testing preparations, they will be careful not to send inferior products to it. Furthermore, it is not necessary to test all samples of any drug procured by the pharmacy, an occasional check-up being sufficient for practical purposes.

In order that the well-trained and experienced pharmacist may carry out the necessary tests for strength and purity of drugs, it is important that the hospital pharmacy have a laboratory equipped for the purpose. Such a laboratory need not be elaborate nor have much expensive equipment. The small original cost for establishing it will be more than compensated for by the savings that will result. There is usually little difficulty in obtaining such a laboratory if the pharmacist can demonstrate he is capable of using it to the advantage of the hospital.

As regards the second of the primary functions of the hospital that affects the pharmacy, namely, the teaching of doctors, nurses and medical students, the pharmacy likewise plays an important rôle. This is particularly true when the

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* Presented before Sub-Section on Hospital Pharmacy, New York meeting, 1937.

[1] New York Hospital and the Department of Medicine, Cornell University Medical College, Cornell Medical Center.

institution is connected with a medical college but is of importance even when it isn't so connected. When the medical student receives his instruction in pharmacy, pharmacology and the principles of therapeutics during his pre-clinical training, he is given a scientific and critical presentation of these subjects. All too frequently, therapeutic ideals thus instilled are later shattered by the irrational therapeutic measures prescribed by a certain number of the physicians on the hospital staff. In this regard it must be realized that in some of the larger hospitals several hundred doctors are members of the staff. In such large groups, a considerable number of physicians will always be found who lack a critical attitude toward the conglomeration of proprietary medications that are being continually thrust upon them by samples, circular letters and other forms of advertising. The various pathological processes that afflict mankind together with their treatment constitute an enormous field for any one man to master. To retain this mastery and to appreciate and utilize new additions to our medical knowledge makes it necessary for the physician to spend a considerable amount of time and effort in reading and studying. Not all physicians have the necessary time or interest to keep up with this work. As a result of this, they are often confused as to what new drugs have been established as having new and definite therapeutic action. Often they are misled by glowing accounts of proprietary medications. In order, therefore, to protect the reputation and finances of the hospitals, it has been necessary in many instances to place restrictions on the use of proprietary medications in these hospitals. These restrictions are usually carried out through a committee conveniently called "the formulary committee" which is composed of representatives of the various clinical departments, the pharmacy, and the department of pharmacology if the hospital is connected with a medical college. The medical representatives are selected because they have developed a critical attitude toward therapeutic procedures. Such "formulary committees" have supervisory powers as regards what drugs shall or shall not be issued from the pharmacy, subject to approval by the hospital administration.

In the New York Hospital, the Formulary Committee functions under the following rules which have been approved by the governing bodies of the institution:

I. Simple official (Pharmacopœial) substances and any in Useful Drugs will be admitted (when requested) unless they have become superfluous.

II. No article will be admitted (except for controlled research) before its therapeutic value has been established.

III. No article of secret composition will be admitted.

IV. No article which is sold under a proprietary name will be admitted under such a name if a substance of identical composition can be obtained under a non-proprietary name.

V. No mixture of two or more active substances will be admitted unless evidence is submitted that the mixture presents therapeutic advantages over the simple substance.

VI. No proprietary article will be accepted before it has been accepted by the Council on Pharmacy and Chemistry of the American Medical Association for inclusion in "New and Nonofficial Remedies."

VII. It is the policy of the Committee to discourage the intravenous and intramuscular injections of substances which should be administered orally.

VIII. The Pharmacist is instructed to supply in emergencies preparations not yet accepted by the Formulary Committee.

IX. The Pharmacist will stock or supply drugs requested on the private or semi-private services even though they have not been accepted by the Formulary Committee.

X. Heads of clinical departments are to be notified whenever any preparation is considered for elimination from the Formulary in order that they may submit their evidence for its retention.

XI. Drugs not accepted by the Formulary Committee may be supplied to the public pavilions if paid for by the department concerned.

XII. The Chief Pharmacist is instructed to issue drugs under rules governing the Formulary Committee subject to the approval of the Medical Board.

XIII. The Formulary Committee shall prepare and issue new editions of the Formulary whenever the Medical Board considers it necessary.

XIV. All actions of the Formulary Committee are subject to approval of the Medical Board.

The hospital pharmacist is always an active and important member of these "formulary committees." In order for him to function effectively on these committees it is important that he be familiar with the medical literature relating to drug therapeutics, that he have a working knowledge of pharmacology in addition to an extensive knowledge of pharmacy, that he have a critical attitude toward proprietary medications and that he be familiar with the actions of the Council on Pharmacy and Chemistry of the American Medical Association in regard to this type of medication.

As the hospital pharmacist plays an important rôle on hospital "formulary committees," it might be well to discuss briefly the problems that confront such committees and the procedures for solving them.

The chief problems of the "formulary committee" are:

1. Proprietary medications.
2. Unnecessarily complicated prescriptions.

In the first place, proprietary medications may be classified into one of three groups:

1. Drugs, the therapeutic value of which has never been established.
2. Drugs that are not essentially different in therapeutic action from simple official (U. S. P.) preparations.
3. Drugs that have a new and definite therapeutic value but have not as yet been in use a sufficient length of time to receive official sanction.

The first step in the deliberation of the "formulary committee" is to classify requested proprietary drugs under one of these three categories. If it should fall under Groups 1 or 2, that is, its therapeutic value has not been established or its action does not differ essentially from simple cheaper official preparations, it is the duty of the "formulary committee" in the interests of economy and rational therapeutics to prevent the use of such preparations in the hospital except for the purpose of controlled research.

As regards the third group of proprietary drugs, namely, those that have a new and definite therapeutic use, it is the duty of the committee to see that they are made available as soon as possible for clinical use. In order that mistakes will not be made in regard to this group of proprietary drugs, careful analyzing of scientific articles concerning the drug is necessary.

The second important duty of the Formulary Committee is in regard to complex formulas. During recent years, there has been a marked tendency toward simplification of formerly used formulas containing numerous active drugs. Nevertheless, there are still physicians who, lacking essential knowledge of pharmacology, present

unnecessarily complex prescriptions. Again in the interests of rational therapy, the formulary committee must eliminate such type of medication if the hospital is to maintain its reputation. The hospital pharmacy has an additional incentive to eliminate such forms of therapy as the work involved in preparing complex mixtures means an unnecessarily large pharmacy staff with resulting increases in expense to the hospital. With few exceptions, therefore, hospital formulas should contain one active drug only besides flavoring, solvents or necessary vehicles for the administration of the active therapeutic agent.

The third function of the hospital that involves the pharmacy concerns itself with research problems involving the use of drugs either in animal experimentation or clinical investigation. This problem resolves itself into two parts:

1. Investigation by the pharmacist.
2. Assistance to physicians engaged in research work.

As regards investigation by the pharmacist himself, I feel that the pharmacist to be successful should from time to time critically examine the various preparations he issues to the hospital for the purpose of determining whether they can be simplified or improved, or whether or not he can manufacture them cheaper or better than can be obtained commercially.

As regards assistance to physicians engaged in research problems, the pharmacist can be of considerable help. He should have the knowledge and interest to assist in the preparation of new drugs and in new and untried methods of administering those of already established therapeutic value. Too often the physician has to enlist the services of commercial pharmacists for this purpose at considerable expense and with often less satisfactory coöperation.

A word should be said here concerning what constitutes a research problem. Too many people consider that merely trying this and that in a haphazard way constitutes research. As far as establishing the therapeutic value of drugs is concerned, research is the carrying out of a study under controlled conditions and under a definite plan with a sufficient number of cases in order that definite information can be obtained as to the therapeutic value of the product.

A word should be said concerning my impression of the future of hospital pharmacies. Will the continued development and improvement of large pharmaceutical firms render it unnecessary or uneconomical for the hospital pharmacy to manufacture or compound medicinal preparations, so that in time the pharmacy will become little more than a storeroom and the pharmacists mere clerks? In my opinion, this will never happen. There are too many preparations that deteriorate on standing; there are too many preparations, such as solutions, that because of their bulk make it uneconomical for transportation from the factory to the pharmacy except in concentrated form; and finally, and most important, the educational demands of a high class hospital make it essential for such institutions to maintain an efficient pharmacy and competent hospital pharmacists.

PROFESSIONAL OPPORTUNITIES OPEN TO THE HOSPITAL PHARMACIST.*

BY CHARLES O. MCCULLOM.[1]

This paper, it is hoped, will present other phases of professional work of which the hospital pharmacist is capable provided he is given the opportunity. The comparatively small financial consideration offered to the average hospital pharmacist for this responsible position has caused many to seek other fields of pharmacy Statistical data published in a current pharmaceutical magazine indicate that the professional pharmacist engaged in hospital pharmacy has little, if any, prospects of future advancement. This, in conjunction with the present financial scale, means that something must be done to improve this condition for the individual hospital pharmacist.

We are equipped with a considerable amount of technical knowledge that might well be applied in the professional field of laboratory analysis as conducted in the hospital. To illustrate of just what this knowledge may consist, take, for example, the analytical balance—this apparatus is of considerable importance in the preparation of many stock solutions used in a hospital laboratory. The handling of pipettes used to measure solution with great accuracy and precision, the proper handling of volumetric and Erlenmeyer flasks, all play a considerable and important part in the routine work as considered in the laboratories. In some of the small hospitals the pharmacist has time and opportunity to make use of this knowledge and skill in assisting with the laboratory work, in addition to the routine drug room duties. The opportunity to do such work and to receive remuneration for it depends, of course, upon the hospital policy and the coöperation of the hospital authorities. More such opportunities might be created if more hospital pharmacists were interested and talked it over with the medical officers responsible. Not only is this work more interesting but the association of the pharmacist with the caliber of men and women who are engaged in this professional field all tends to make his assignments very stimulating.

The pharmacist who is fortunate in having some few hours free each day is in a position to apply ability that has been somewhat dormant, that is, of course, with the understanding that a plan be presented to the proper individuals, indicating that the technical training might be useful in the hospital laboratory work.

The duties as demanded by a hospital laboratory require just so much time in order to properly carry on this work. These so-called laboratory duties as mentioned from time to time may be somewhat confusing; therefore a brief outline of what analyses are frequently done in the hospital will be discussed.

First, the analysis of urine as conducted in a hospital consists for the most part of routine examination for the color, acidity, specific gravity, albumin, sugar or acetone, and also the microscopic study of the urine sediment. The amount of time required in doing these analyses depends a great deal on the size and type of hospital. Such analyses are very often done by a trained technician or some intern and in some rare cases the pharmacist. The pharmacist who may wish to acquire the proper training for this work can do so by taking a course of urine analysis either at a College of Pharmacy or possibly under the supervision of the laboratory director or his assistants.

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Second, the routine analyses of blood are very apt to differ with the type of hospital. The outline as here described in brief is based on experience gained by doing this work for the past few years. The most common routine analyses of blood consist of doing a red and white cell count, determining or finding the Hb content, and finding the amount of sugar and non-protein nitrogen present. Less frequently other analyses of the blood are requested, the technique of which may be acquired both by observation and instruction, as, for example, the estimation or normal or abnormal amounts of calcium bromides, chlorides or phosphates present in the blood serum. A new patient recently admitted may be found by these laboratory analyses to have an abnormally high bromide concentration in his blood serum and the pharmacist who is doing these tests has the interesting opportunity to see for himself the rapid decrease in the serum bromide after the treatment with extra sodium chloride. This illustrates some of the fascination in doing this work and can hardly be equalled in other fields of pharmacy. A similar situation is met when doing the analysis of a blood indicating diabetes—very quickly insulin is ordered and then administered to this patient with the result of a lowered blood-sugar content. Take also the blood that indicates a presence of either secondary or primary anemia as observed by the pharmacist-technician; he receives the order to issue either liver extract or some iron preparation at once. Several weeks later another blood analysis is done on the patient and very often the hemoglobin content or red cell count becomes elevated. The pharmacist not only has the opportunity to see that this does occur but has the interesting experience of observing in detail the different effects of various preparations.

Third, as the large hospital requires most of the pharmacist's time the chance of trying to do the work as described is nearly impossible. There is the opportunity, however, of teaching or instructing the student nurses in the fundamentals of Materia Medica. The benefits observed from this experience are many, but one of the more important is the fact of educating oneself by keeping in touch with the new and more recently discovered drugs. The time required in preparing the material for a lecture can be arranged at the convenience of the pharmacist. As a rule the lecture will require about one hour several days a week. This course in Materia Medica should be made the responsibility of every pharmacist employed in a hospital which maintains a training school. This is not the case at present in many hospitals, such instruction being done by either a graduate nurse or intern, both of whom may be sincere and earnest in their efforts but can hardly meet the quality of instruction that could be offered by the hospital pharmacist. My knowledge is not only based on the teaching of this subject but, better still, in talking with the affiliating nurses from other hospitals and discussing with them the methods that had been used in presenting this course at their hospital. The information as gathered leads me to believe that much trouble centers around the fact that many instructors have little interest in their subject. Also for some unexplained reason this subject of Materia Medica was not considered important as compared with chemistry, bacteriology or practical nursing, and was therefore treated accordingly. This attitude for such an important science might very well be one explanation for some of the mistakes made in the administration of drugs in the hospitals to-day. With these few facts in mind the pharmacist employed

in a hospital should make a real effort to undertake this responsibility that cannot only prove to be very interesting and educational but also a means of adding some prestige to his position.

A pilular compound consisting of ability, professional responsibility, time and opportunity all rolled together, may prove to be the tonic necessary to treat the chronic condition of monotony often present in our hospital pharmacies to-day.

THE OUTLOOK FOR HOSPITAL PHARMACY.*

W. B. SMITH.[1]

For the past nine years I have been dividing my time between a hospital pharmacy and a retail drug store. The hospital with which I am connected has only ninety beds, which accounts for my not being employed full time.

My experiences during this nine-year period have impressed me daily with the differences between hospital pharmacy and that of the retail store. These differences are known to all of you and hence need not be named specifically.

It is my firm belief, however, that hospital pharmacy will play a large part in redeeming professional pharmacy. The literature for the past year shows that hospital authorities are thinking more about pharmacy now than they ever have in the past. They have always known that the administration of medicine is important. They are now beginning to realize that medicines should be carefully prepared by people who are properly trained in this field. They are attaching more and more significance to the fact that the pharmacy should be properly equipped and should be conducted by a properly trained pharmacist rather than by nurses and interns.

Recent articles in the JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION and the *American Journal of Pharmaceutical Education* show that our colleges of pharmacy are considering hospital pharmacy more seriously, and in some cases are making changes in their courses in order that their graduates may be better trained for hospital work.

The employment of pharmacists by hospitals which are large enough to justify this, will create professional positions for several thousand. This will add to the usefulness and efficiency of the hospital and will help establish pharmacy as a profession in the minds of the interns who go into the field each year for the practice of medicine.

I am glad this sub-section on hospital pharmacy has been formed. It should be highly useful by enabling hospital pharmacists to get together annually and discuss their problems. I hope that at the proper time the section will consider preparing a manual of approved methods of procedure in the manufacture of sterile solutions and other products which require skill and precision.

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* Presented before Sub-Section on Hospital Pharmacy, New York meeting, 1937.

[1] Stuart Circle Hospital, Richmond, Va.

THE PROBLEM OF APTITUDE TESTING IN PHARMACEUTICAL EDUCATION.*

BY SAMUEL S. LIBERMAN.[1]

The development and application of the psychological test, frequently called the intelligence test, has been very great during the last two decades. Although the psychological test had previously been utilized by Cattell and others, Binet's announcement in 1908 of "a scale for measuring intelligence" occasioned quite a stir. Various improvements on the original Binet test were made and various modifications were devised. It was not until 1917 that the full significance of these tests was made apparent. At that time, the United States entered the World War and the War Department decided to utilize psychological tests on the recruits as a rapid method of separating the men on the basis of their mental equipment. A. S. Otis, who at that time had already developed a series of tests, donated to the army the results of his efforts (1). Two batteries of tests were developed using the Otis tests as bases, and were denoted as the "Alpha" and "Beta" modifications. The results were, to say the least, interesting. The use of these tests naturally served to direct an enormous amount of public interest toward them. After the war, the Army Alpha, as the test was known, was used in industry as a means of selection of employees. The indiscriminate utilization of these psychological tests as a means of forecasting aptitude resulted in failure and disappointment. The entire testing movement as a result fell into disrepute.

American educators, however, had long felt that a test or series of tests of this type could well be used as a means of determining to some extent the mental equipment of the great body of students in the secondary schools and colleges of this country. The idea caught, with the result that we have available a large body of data on intelligence tests and intelligence testing.

We are all well acquainted with the rapid rise in the use of the general intelligence test as a means of predicting academic success. It has also been used as an instrument of guidance in the training of young men and young women in the secondary schools. But the intelligence test, as such, is an indifferent instrument and quite inadequate as a means of predicting aptitude in specialized fields.

A great number of studies have been made in which ratings received on intelligence tests have been correlated with grades received in the various subjects on the secondary and college levels. Unfortunately, some of the earlier studies are of little value, due to the subjectivity of the methods of grading in the secondary schools and colleges. Nearly every type of mental test and educational performance test has been used as a means of obviating this discrepancy. The results have been tabulated and correlated, so that we now have at hand several series of standardized tests for which norms have been established. We can see the importance which has been attached to the results obtained on these intelligence tests by noting that they are used by a large number of colleges for various purposes.

In an attempt to overcome pupil variation, a modified form of performance test was devised, and called a placement test. This specialized test has been prepared for many subjects. Cornog and Stoddard, of the University of Iowa, prepared

* Presented before the Section on Education and Legislation, New York meeting, 1937.

[1] Associate in Chemistry, Columbia University, New York College of Pharmacy.

one for chemistry, " . . .with the object of getting a better prediction of student performance in freshman chemistry than is ordinarily secured by the general intelligence tests" (2). The coefficient of reliability of these tests is much higher than that obtained by the use of intelligence tests alone. While approaching it, these tests do not determine special aptitudes. As Hull (1) puts it, ". . . . . if a test is to be of any particular value, it must enable us to forecast a *particular* aptitude or group of aptitudes . . . . . "

Special tests, known as aptitude tests, have already been devised for various trades, as well as for various academic subjects. By means of these tests, characteristics peculiar to a certain trade or subject can be measured in an individual. A Scientific Aptitude test has been devised by Zyve of Stanford University (3). Special aptitude tests in engineering, medicine and law are used by various colleges, apparently with success, as a means of selection of prospective students. It seems, therefore, that it should be possible to devise a battery of tests to determine aptitude for pharmacy.

Objection will at once be raised on the ground that pharmacy, unlike medicine or law is more of a business than a profession. It is not the function of this paper to settle this argument. But it may be pointed out that several studies have been made in an effort to establish a correlation between scholarship and success as measured by salary and that the results have been positive. One study, made by Bridgman in 1930, involved the correlation of success of 3806 college graduates in the employ of the Bell Telephone System, with their scholastic standing. He found that high scholarship was an important factor in later success (4).

The solution of this problem is not simple. Dogmatism must be avoided and in formulating any program involving the application of tests of this nature, a scientific attitude must be maintained. What we are looking for is a battery of tests which will enable us to predict with fair success an aptitude for pharmaceutical practice. No one single test can do this. It is possible that an indication of pharmaceutical aptitude may be predicted by means of

1. Determination of general scholastic aptitude and correlation with grades received in college and on state board examinations.
2. Determination of specific ability as measured by a special battery of tests, previously standardized and correlation with grades received in college and on state board examinations.

Admittedly, we are not in a position to predict success in later life in the practice of pharmacy. We should, however, try to correlate data available. But we should also bear in mind the pronouncement recently made by Dr. Kitson of Teachers College, Columbia University. "A test," he said, "may help an employer choose the best two out of a hundred applicants for a certain position . . . . . "

At this time, I wish to propose a possible series of tests, some of which are already available. This series would include tests for

1. Reading and comprehension.
2. Manipulation.
3. Reasoning and interpretation of directions.
4. Mathematical ability (particularly in arithmetic).
5. Inventiveness.

The reasons for this series, for the most part, are obvious. The ability to read and to understand what has been read is of great consequence. The ability to

properly manipulate apparatus and, as a corollary, compound prescriptions is probably the most important item. In order for the pharmacist to compound prescriptions properly, a certain amount and kind of innate reasoning ability is necessary, which is related in some way to the fifth of the series, inventiveness. My reason for the inclusion of a test for mathematical ability may appear odd, but in my experience, I have found that students deficient in the ability to use arithmetical processes are poor material in so far as their records at pharmacy college are concerned. I need not emphasize the importance of this in connection with the practice of pharmacy.

What is also required is an efficient job analysis involving the duties of the professional pharmacist, which is necessary as an aid in the construction of a suitable aptitude test. Work along this line has already been carried out and the results published by Charters, Lemon and Monell as the "Basic Material for a Pharmaceutical Curriculum."

It must be remembered that a project of this kind, to be of value, must be carried on for a period of not less than ten years, probably longer. Furthermore, it will be necessary to gain the whole-hearted support of the Colleges of Pharmacy and as well, that of pharmaceutical associations. Without coöperation, this work cannot be done as it should be.

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ALONZO ROBBINS, PENNSYLVANIA'S NUMBER ONE PHARMACIST.*

BY JOHN E. KRAMER.[1]

Very often a pharmacist who has established himself firmly in professional circles in his state, and who has taken great interest and much responsibility in his state organization, earns the title of "leading druggist," "foremost pharmacist," or "the state's most prominent man in pharmaceutical affairs." The subject of this paper, Alonzo Robbins, was, in truth, all of these, for his Pennsylvania State Certificate, entitling him to practice as a registered pharmacist, has the distinction of bearing the Number One.

It was in 1887, on June 23rd, that the Governor of the great Keystone State created a Board of Pharmacy for the purpose of examining and licensing those who wished to pursue the art and the science which treats of medicinal substances. Until that time there had been no state supervision, and little or no local looking-after of pharmacists, although Philadelphia had exercised some control over its druggists.

Naturally, the first Pennsylvania State Board needed a leader, and Alonzo Robbins, who was then in business for himself at 11th and Vine Streets, in Philadel-

* Presented before the Historical Section, A. PH. A. meeting, New York, 1937.

[1] Registrar, Philadelphia College of Pharmacy and Science.

phia, was appointed president. One of the first duties of the honorable and honored group of men was to register all of the properly qualified pharmacists then practicing within the State's borders. This was done, and handsomely engraved, sealed, signed and numbered certificates were duly issued. By a queer coincidence, Alonzo Robbins, president of the Board, received Certificate Number One.

Pottstown, Pa., some few miles to the west of Philadelphia, was Alonzo Robbin's birthplace, in 1834. He came from there to Philadelphia and later entered the Philadelphia College of Pharmacy, from which he graduated in 1855, with the degree of Graduate in Pharmacy, after having completed a two-year course of study. His graduation thesis was a treatise on "The Optical Properties of Fecula, a Form of Starch." There were but twenty-six members in the graduating class with which Robbins received his coveted diploma. Strangely enough, three of the twenty-six later became trustees of their Alma Mater, and Robbins was one of them, having been elected to the Board in 1878 and serving until his death in 1896. He was further honored by his College in 1889 with the honorary degree of Master in Pharmacy.

ALONZO ROBBINS.

His successful activities as a retail pharmacist were supplemented by the detailed duties required of him as State Board President, until he resigned in 1895, and as College Trustee. He helped found the Pennsylvania Pharmaceutical Association and, in addition, was a member of the committee appointed by the Philadelphia College of Pharmacy to assist the Pharmacopœia Revision Committee of 1880. Alonzo Robbins' chief work with this latter group was in the field of fluidextracts, and the *American Journal of Pharmacy* for 1883 records his carefully prepared reports, in which he minces no words over the fact that the Revision Committee did not accept all of the suggestions offered by his College Committee. For intsance, he states, "The decision of the Committee on Revision to make the finished product represent the drug volume for weight, appears to be an unnecessary exception to the general plan of the Pharmacopœia..... It may be said of several of the eleven (newly added extracts) that they are of no more value than some of the ten which were stricken off ..... Danger of injury from heat and loss of activity by precipitation have been over-estimated by writers on fluidextracts." With all due respect to the gentleman and scholar, it may be conjectured that anyone wearing the hirsute adornments that he did, had daily call upon the strength of his own convictions.

His store, on a corner once the center of better Philadelphia, is now a restaurant in one of the decidedly poorer sections of the "City of Brotherly Love." During some recent renovations by his proud descendants, his diploma, his honorary degree, his Pennsylvania Certificate Number One and his certificate of appointment to the State Board, all nicely framed and well preserved, were uncovered. They are soon to be presented to the Museum of the Philadelphia College of Pharmacy and Science.

MINNEAPOLIS, CITY OF LAKES.

Minneapolis' attractions are not surpassed by those of any city in the world. It is the Gateway to Vacation-land, with an average summer temperature of 70 degrees. A group of ultra-smart hotels invites you to restful ease, while a few blocks away you may view the giant flour mills at St. Anthony's Falls, which were discovered in 1680 by Father Louis Hennepin.

No other city has so many lakes within its city limits, where out-door sports may be indulged in; shopping districts offer the products of all countries; and here is located the University of Minnesota, fourth largest in America.

Commercial, financial, educational and cultural center of the Northwest, Minneapolis now ranks fifteenth in size among the cities of the United States.

The Nicollet, Headquarters Hotel, A. PH. A. Convention, August 21st to 27th, located at Nicollet at Washington, offers the following rates: Single Rooms, with and without bath, $2.50 and up; Double Rooms, with and without bath, $4.00 and up. Among other hotels are: Andrews, Field, Radisson, Sheridan, West, Vendome.

College of Pharmacy, University of Minnesota.

Lake of the Isles.

PROCEEDINGS OF THE LOCAL BRANCHES

"All papers presented to the Association and Branches shall become the property of the Association with the understanding that they are not to be published in any other publication prior to their publication in those of the Association, except with the consent of the Council." —Part of Chapter VI, Article VI of the By-Laws.

ARTICLE III of Chapter VII reads: "The objects and aims of local branches of this Association shall be the same as set forth in ARTICLE I of the Constitution of this body, *and the acts of local branches shall in no way commit or bind this Association, and can only serve as recommendations to it.* And no local branch shall enact any article of Constitution or By-Law to conflict with the Constitution or By-Laws of this Association."

ARTICLE IV of Chapter VII reads: "Each local branch having not less than 50 dues-paid members of the Association, holding not less than six meetings annually with an attendance of not less than 9 members at each meeting, and the proceedings of which shall have been submitted to the JOURNAL for publication, may elect one representative to the House of Delegates."

Reports of the meeting of the Local Branches shall be mailed to the Editor on the day following the meeting, if possible. Minutes should be typewritten with wide spaces between the lines. Care should be taken to give proper names correctly and manuscript should be signed by the reporter. *Please advise us of changes in Roster and mail reports promptly.*

BALTIMORE.

The March meeting of the Baltimore Branch, A. PH. A., was held at the University of Maryland, School of Pharmacy, Thursday, the 24th, at 8:15 P.M. This was a very important meeting, the program being somewhat unusual, as a prominent Baltimore Urologist, Dr. Lloyd G. Lewis, of the Johns Hopkins Medical School, was guest speaker. He discussed phases of the venereal disease problem, which is of interest to every pharmacist, as the U. S. Public Health Service has called on the A. PH. A. membership for aid in carrying out its program. Retail pharmacists are frequently called on for advice regarding treatment in this and other infectious diseases. A better understanding of these diseases, and the unfortunate sequelæ which follow improper methods of treatment, is of great value to pharmacists who wish to aid in promoting the general objectives sought in the national public health campaign.

At the conclusion of the regular meeting refreshments were served.

ROBERT S. FUQUA, *Secretary.*

NOTE: The above report was overlooked and is published at this time in order that the Branch may receive due credit.

MICHIGAN.

The April meeting of the Michigan Branch of the A. PH. A. was held Tuesday, the 26th, in the Wayne County Medical Society Building, following the usual steak dinner. The Student Night Program attracted an exceptionally large number of students from the various colleges of pharmacy. More than 125 students in pharmacy were present when the meeting was called to order by Vice-President Robert L. Church, in the absence of President Earl Soop, due to illness. The minutes of the previous meeting were read and approved.

Robert Church, College of Pharmacy, University of Michigan, presented a most constructive paper entitled, "The Reference Library of the Pharmacist." He pointed out the value and necessity of a reference library to both pharmacist and physician. An easy and simple means for obtaining an up-to-date reference library was outlined.

The second speaker, Miss Marjorie Manring, College of Pharmacy of Wayne University, presented a very interesting paper on "Paracelsus." The life of Paracelsus reads like a fairy tale. His philosophy and ideas were absolutely contrary to those of the scientist of to-day.

Carl Fisher, Institute of Technology, College of Pharmacy, read a paper on "Anesthetics." A vast amount of preparation and research were necessary in getting together the facts portraying the rapid strides and many improvements in the administration of anesthetics, which were supplemented by L. W. Rowe.

Robert Olson, College of Pharmacy, Ferris Institute, presented a most timely and much discussed subject, "Why I Desire to Become a Professional Pharmacist." In his paper Mr. Olson

brought out the many advantages that await the student who desires to become a professional pharmacist.

A general discussion followed, led by H. A. K. Whitney, Chief Pharmacist, University Hospital, Ann Arbor, and member of the Michigan Board of Pharmacy. Mr. Whitney complimented the students highly, as did also L. W. Rowe, H. B. Lewis and R. L. McCabe. J. H. Webster illustrated with a story the vast amount of knowledge that is sometimes required of a pharmacist to make a small sale. His illustration proved the necessity of a reference library, to the pharmacist.

It was moved by R. L. McCabe that the name of the Branch be officially changed to the Michigan Branch as being a more suitable title since the Branch represents the entire state of Michigan. The motion was seconded and carried. Mr. McCabe moved, also, that the Michigan Branch go on record to bring the A. PH. A. Convention to Detroit in 1939, which motion was seconded and carried.

Dean H. B. Lewis outlined the program for a joint meeting of the Branch with the Pharmaceutical Conference to be held in Ann Arbor, May 18th.

The meeting adjourned at 9:30 P.M.

BERNARD A. BIALK, *Secretary.*

PHILADELPHIA.

The April meeting of the Philadelphia Branch, A. PH. A., was held in the Museum of the Philadelphia College of Pharmacy and Science, Tuesday, April 12, 1938. The meeting was called to order by Dean Kendig, who turned the gavel of office over to the new president, Dr. Viehoever.

President Viehoever welcomed the many members who had turned out for this meeting and asked for their continued support. He expressed the hope that the Branch activities might be so conducted as to interest the younger men in pharmacy as well as the students of Pharmacy, in the Philadelphia area. It was pointed out that our membership does not include a very high percentage of eligible persons in this area, and President Viehoever indicated that plans were being made to bring as many as possible of these individuals into affiliation with the ASSOCIATION.

A list of twenty proposed Committees to carry on the work of the Branch was distributed to the members, together with the names of the personnel of these committees.

The program for the evening represented a progress report of the workers in the Gross Laboratory for Biological and Biochemical Research of the Philadelphia College of Pharmacy and Science. Dr. Viehoever introduced Dr. N. Tischler, who spoke on "Methods for Testing Insecticides on Moths, Flies and Carpet Beetles." Dr. Isidore Cohen discussed "The Use of Daphnia Magna as a Test Animal in the Detection of Vitamin E," pointing out that at present the qualitative aspects are well established and that work is being done to perfect the quantitative methods. Mr. A. Taransky and Mr. N. Sokoloff discussed "The Use of Daphnia in Mass Experiments for Testing Digitalis and Its Preparations." Mr. G. Quimba discussed "The Use of Daphnia in Testing Snake and Bacterial Poisons," and explained the technique of micro-injection of solutions directly into the body of the animal. Mr. C. Matthews showed a film by Dr. Ivy showing a method for testing Chologogues. He later demonstrated the Stethographone, an apparatus for amplifying the sound of the heart beat.

Dr. Kendig, chairman of the Committee on Biography, read a short sketch on the life of Dr. H. C. Christensen, who has been nominated to receive the Remington Medal for 1938.

Dr. E. F. Cook, chairman of the U. S. P. Revision Committee, announced that the U. S. P. has been translated into Spanish and has been adopted in certain of the Central and South American Republics, and will serve as a standard for revision of the Pharmacopœia in certain countries having their own standard book.

W. W. McNeary reported that plans are under way to organize the pharmacists of Philadelphia hospitals into a group. He expressed the hope that when the new organization is formed, provision will be made for its affiliation with the Branch.

The meeting adjourned at 10:45.

ARTHUR K. LEBERKNIGHT, *Secretary.*

MAY.

The May meeting of the Philadelphia Branch, A. PH. A., was held on Wednesday, May 18th, in the Auditorium of the Philadelphia College of Pharmacy and Science. The meeting was

called to order by President Viehoever at 8:30 P.M., and the minutes of the previous meeting were read and approved.

Mr. W. W. McNeary gave a brief report on a meeting which was held on May 6th to organize a group of hospital pharmacists in Philadelphia. He stated that at this meeting it was decided to form an organization to be affiliated with the A. PH. A. and the Local Branch. Mr. Frazer of the Presbyterian Hospital is serving as temporary chairman of the group and Mrs. Ida Champaine of the Northern Liberties Hospital is temporary secretary. President Viehoever called upon Mrs. Champaine, who outlined the proceedings of the initial meeting of the hospital group and expressed the hope that an organization might be worked out which will be mutually beneficial to the hospital pharmacists and the Branch. The secretary read a letter from Secretary Kelly of the A. PH. A., in which he expressed deep interest in the formation of the hospital pharmacists' organization and offered to give all the assistance he possibly could, in this venture.

President Viehoever introduced Mr. James Horton, Chief Examiner for the Federal Trade Commission, who discussed the Wheeler-Lea Law which controls the advertising in every form, except the label, including broadcasting, used in the promotion of sales of foods, drugs, cosmetics and devices. Mr. Horton emphasized that the act was not to be construed as dictatorial in nature; that its purpose was to insist on truthful advertising, and that legitimate firms or individuals marketing safe and effective products, in good faith, would not find it difficult to operate within the law.

Dr. E. Fullerton Cook, Chairman of the U. S. P. Revision Committee, then discussed some of the important provisions of the proposed new Food, Drug and Cosmetics Law now before Congress. Among the most recent amendments to the Bill is one providing that manufacturers, before placing a new drug on the market, must obtain a release from the Food and Drug Administration. Dr. Cook announced that a new Supplement to the U. S. P. was about to be released.

General discussion followed both speakers. Mr. Horton and Dr. Cook were accorded a rising vote of thanks for their excellent addresses.

The meeting adjourned at 10:30.

ARTHUR K. LEBERKNIGHT, *Secretary.*

ST. JOHN'S UNIVERSITY STUDENT BRANCH.

DECEMBER.

On Dec. 17, 1937, the Branch assembled for its meeting, Miss Agnes Sullivan presiding. The minutes of the last meeting were read and accepted. The chairlady introduced Mr. M. Dubinbaum of the Committee on Progress of Pharmacy, who presented an interesting paper on "The History and Uses of Chlorine and Its Products."

The next speaker of the evening was Dr. Julius Chasnoff, educator and practicing physician, whose topic was "The Importance of Biological Science to Medicine and Pharmacy."

Dr. Chasnoff discussed Elixir of Sulfanilamide, Vitamins, Research Work on Laboratory Animals, Endocrine Products, etc. His discussions were highly interesting and educative.

CATHERINE BOSIO, *Secretary.*

JANUARY.

The election of officers for the year took place on January 5, 1938, with the selection of: Dorothy E. Cimarosa, *President;* Harry Leifer, *Vice-President;* Sheldon Linet, *Treasurer;* Catherine Bosio, *Secretary.*

CATHERINE BOSIO, *Secretary.*

FEBRUARY.

At the February meeting, held on the afternoon of the 16th, the Branch was addressed by Dr. Robert G. Page of the Burroughs-Wellcome Co. on the Subject of "Vitamins." His talk was supplemented by a series of lantern slides which depicted the structural formulas of those vitamins which have been synthesized and which also showed the changes in body tissue resulting from insufficiency of vitamins in the diet. "Since the specific usefulness of vitamins is not yet definitely known," he said," vitamins are often administered in such combinations as ABDG instead of singly."

CATHERINE BOSIO, *Secretary.*

MARCH.

On March 30th, Dr. Ralph Clark, Ph.D., of Merck & Co., spoke before the Branch on

"The Arsphenamines," their use, the importance of making solutions of them rapidly to prevent oxidation, and demonstrated the technique of preparing such solutions.

CATHERINE BOSIO, *Secretary.*

APRIL.

A special meeting was called on Thursday, April 28th. There was a large attendance, and due to the nature of the meeting the official formalities were dispensed with. An introduction to the topic of the meeting "The Story of Quinine," which included mention of the human history of the drug, its uses and derivatives, was given by Professor Corcoran. A motion picture entitled "Malaria" was next presented through the courtesy of the Winthrop Chemical Company, which showed the ravages of the disease, its causes, effects, cure and preventatives by actual pictures taken in Georgia and the laboratory. A general discussion followed in which many questions were asked by the different students of Professors Corcoran and Monte-Bovi. A student display on Quinine, its various forms, commercial preparations and typical prescriptions with an accompanying pictorial chart displaying the historical story of the drug and its malarial associations was next revealed for inspection by all present. Credit for the display goes to these Sophomores: M. Warner, Carmine Martino, Frank Torchia, Anthony D'Agostino and J. B. Friedberg.

CATHERINE BOSIO, *Secretary.*

MAY.

The closing meeting of the year was held at the school on May 12, 1938, Mr. Harry Leifer acting as chairman. After the preliminary procedure, Mr. Aaron Friedenthal, of the Committee on Progress of Pharmacy, reviewed the latest research in "Buffer Solutions" with especial reference to their use in Ophthalmology.

The Rev. Father Walsh, president of St. John's University, next addressed the meeting. He commended the group for its interest in the AMERICAN PHARMACEUTICAL ASSOCIATION, holding that the highest type of professional worker will always align himself with some organization that promotes the advancement of his profession. "This type of activity," he said, "is without end for always new discoveries and new learning are to be added to man's knowledge."

This view was shared by Dr. Ernest Little, dean of Rutgers University, College of Pharmacy, and chairman of the Committee on Student Branches of the A. PH. A., who was introduced by Dean John Dandreau. For example, he pointed out that a student of Organic Chemistry studies the first five or six members of the aliphatic series of hydrocarbons, whereas the members of this series can conceivably number several hundred thousand or even millions. "To widen the scope of our knowledge is one aim of the A. PH. A.," he stated; "to represent the pharmaceutical profession in national legislative matters is another, and it is lamentable that so small a percentage of the pharmacists of the nation has joined the body." Turning to conditions in retail pharmacy, Dr. Little declared that in his experience poor business was usually the result of poor business practices and related some incidents to prove this. He then congratulated the Branch on rounding out its college program by including in it extra-curricular activities.

A rising vote of thanks for our distinguished guest speakers concluded the meeting.

CATHERINE BOSIO, *Secretary.*

The *New Jersey Journal of Pharmacy*, for June 1938, published the following educational editorial advertisement, written by Mr. Robert S. Sherwin, president of Petty's Pharmacy, Newark, N. J.:

"During 1933 twenty thousand people died as the result of appendicitis, a mortality which is astonishing when one knows that most of these persons need not have died. Prompt medical attention is the safe and simple rule which would have saved thousands of men, women and children to long life, success and happiness.

"The really dangerous thing about appendicitis is the tendency of the average person to treat himself when a pain appears. Never take a cathartic or any medicine except on a physician's advice. When an abdominal pain appears, see your doctor immediately. If the pain arises out of simple indigestion, he will say so; if it is more serious he also knows what steps to take. Follow his advice even in the matter of the selection of a druggist to fill his prescription."

ASSOCIATION BUSINESS

AD INTERIM BUSINESS OF THE COUNCIL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION, 1937–1938.

Office of the Secretary, 2215 Constitution Ave, Washington, D. C.

LETTER, NO. 8.

May 13, 1938.

To the Members of the Council:

50. Use of the Text of the N. F. VI. Motion No. 17 (Council Letter No. 6, page 160) has been carried and Professor Leake and Dr. Geiling have been so advised.

The following communications have been received from Chairman DuMez of the Committee on Publications:

"I have looked over the request of Mr. B. T. Howiler of the Peralta Hospital, Oakland, California, to use portions of the text of the N. F. VI in the preparation of the Peralta Hospital Formulary and find nothing unusual in this request. I, therefore, recommend that permission be granted Mr. Howiler to use the text of the N. F. VI for this purpose and that no charge be made for same."

"In response to the letter of Chief Pharmacist, Helen Glucksman, of the Orange Memorial Hospital, Orange, N. J., it is recommended that permission be granted to use portions of the text of the N. F. VI in the preparation of a hospital formulary and that no charge be made for this grant."

(*Motion No. 20*) It is moved by DuMez that permission be granted to B. T. Howiler, Oakland, Calif., and Helen Glucksman, Orange, N. J., to use portions of the text of the N. F. VI in the preparation of the Peralta Hospital Formulary and the Orange Memorial Hospital Formulary, respectively, with the customary acknowledgment and for value received.

51. Loyola University Student Branch. Motion No. 18 (Council Letter No. 7, page 271) has been carried. The Loyola University Student Branch held its opening meeting on May 5, 1938.

52. Election of Members. Motion No. 19 (Council Letter No. 7, page 271) has been carried and applicants for membership numbered 214 to 338, inclusive, are declared elected.

53. A. Ph. A. Laboratory. The following communication has been received from Chairman Gathercoal of the Committee:

"The Committee on Laboratory held a meeting at the AMERICAN INSTITUTE OF PHARMACY on Tuesday, April 5th, with the following members present: Doctors Beal, Cook, Gathercoal, Hilton, Kelly, Rosin and Krantz. After a careful review of the duties entrusted to it and the progress made toward carrying them out, the Committee wishes to submit the following report and recommendations.

"Referring to Council Letter No. 5, and to the Laboratory Budget:

RECEIPTS.

"The gift for a Special Research on Calomel Ointment and the U. S. P. Contribution to the Color Research have been paid, and arrangements have been completed for the use of both sums for the purposes indicated.

DISBURSEMENTS—PERMANENT INVESTMENT.

"*Item 1.*—The preparation of the rooms has been practically completed and the total cost, which will be reported later, will be approximately the sum estimated, $4000. It has been necessary to make certain modifications in the plans which will also be covered in a supplemental report.

"*Item 2.*—The laboratory furniture was delivered and installed during April and May. It was necessary to make some modifications with respect to the details of the 21 articles mentioned, and the total cost will not exceed the sum estimated.

"*Item 3.*—Some of the office furniture has been purchased and delivered. The remainder of the items will not be purchased until later but the budget item will not be exceeded.

"*Item 4.*—The selection of permanent apparatus was given careful consideration from the standpoint of present and future requirements, and lists covering apparatus were prepared. Such apparatus will be purchased as the budget provisions will permit.

MAINTENANCE EXPENSES.

"*Items 5 to 11.*—The expenditures under these items were reviewed and they indicated that the budget appropriations will be sufficient. Special attention was given to Item 9 and the lists of glassware, drugs, chemicals, reagents and other supplies were revised to keep the cost within the budget appropriations for 1938.

SPECIAL RESEARCH GRANTS.

"*Item 12.*—Chairman Gathercoal reported on the grants so far made and the progress of the work under each grant and on the grants which are under consideration.

"The Committee then inspected the rooms for the Laboratory and reviewed the arrangements for its transfer and installation.

"With the progress so far made, it is expected that the Laboratory will be removed to the new quarters about June 15, 1938.

"The Committee was also to 'study the policies and personnel of said laboratory and recommend to the Council at its earliest convenience, such changes and additions to the By-Laws of the AMERICAN PHARMACEUTICAL ASSOCIATION as may be needed to give recognition to said laboratory as one of the AMERICAN PHARMACEUTICAL ASSOCIATION'S activities; to set forth the scope and policy of this laboratory; and to provide for its personnel and maintenance. (See Council Letter No. 19, 1936–1937, page 1055).

"The Committee recognizes that certain amendments to the By-Laws as referred to above will be advisable and probably necessary but, after careful consideration, believes that action on such amendments should be deferred until longer experience has been had in the operation of the Laboratory and the requirements in this respect are more fully understood. The Committee, therefore, submits herewith a set of Rules for the Supervision of the Laboratory with the request that they be put into effect by Council action rather than be amendments to the By-Laws of the ASSOCIATION in the belief that they will effectively serve the present requirements. It is the conclusion of the Committee that the membership of the permanent Committee on Laboratory should not exceed five, that the term of appointment should be five years, and that the Chairman of the U. S. P. Committee of Revision, the Committee on National Formulary and the Committee on Recipe Book should be ex-officio members of the committee. Such an arrangement will cause no vacancies in the membership of the present Committee since Chairmen Cook and Gathercoal are now full members of it and would become ex-officio members of the permanent Committee. It is also the conclusion that the present Committee should become the permanent Committee with the changes indicated, in order to provide a more continuous policy of supervision than if all the members were replaced. In the belief that the Council will welcome suggestions as to the persons that are well qualified to fill the two vacancies mentioned, in case the proposal is approved, the present Committee recommends that Carson P. Frailey of Washington, D. C., and Charles B. Jordan of La Fayette, Ind., be elected with George D. Beal, John C. Krantz, Jr., and Joseph Rosin, members of the present Committee, as the members of the permanent Committee on Laboratory, with George D. Beal as the Chairman of the Committee for the first year. It is also recommended that in order to provide a continuous policy of supervision of the Laboratory the persons named be elected for terms of five, four, three, two and one years on an alphabetical arrangement, and that in future one member be elected each year to serve for five years.

"These rules and recommendations are submitted at this time rather than during the Minneapolis meeting, because the Committee is convinced that the changes in the direction and control of the Laboratory as recommended should be made at the time the Laboratory is transferred to Washington rather than to have the present Committee continue the direction until after the annual meeting of the ASSOCIATION with a consequent interruption in responsibility. It is understood that the three men now employed in the Laboratory in Chicago will be transferred to

Washington, that the Research Assistant now located at the Bureau of Standards on the color standardization work will be attached to the Laboratory and that Chairman Gathercoal will continue to supervise the Laboratory until the permanent Committee shall secure the services of an administrative head. This arrangement will provide for four laboratory workers, an administrative head, a secretary and a technician-janitor; or a total force of seven people.

"This Committee is convinced from the experience so far had, that the grants from the income of the Research Fund should be so made as to fully support the Laboratory program and on recommendations which reach the Council through the permanent Committee on Laboratory. This procedure does not require an immediate amendment to the By-Laws since they now provide that the 'Committee on Pharmaceutical Research shall endeavor to promote research along pharmaceutical lines and shall advise the Council as to the use of the research funds of the Association' and the two Committees can coöperate in this purpose.

"It is the opinion of this Committee that the scope and policies of the Laboratory were sufficiently set forth for the present requirements in the Introductory to Council Letter No. 5, 1937–1938, and that if the statements therein require amplification, the new Committee on Laboratory will be better prepared to do so after some experience in the actual operation of the Laboratory in Washington.

"Since provision has been made for installing and equipping the Laboratory and for its personnel and maintenance, this Committee requests that the Council will take prompt action on the Rules as submitted and on the election of the permanent Committee, it being understood that if the action is favorable, a meeting of the permanent Committee will be held at about the time the Laboratory is transferred, to take over the work of the present Committee and that this Committee will then cease to function except to submit its final report to the Council during the next annual meeting.

"This Committee is confident that if the arrangements for supervision as proposed are put into effect, the Laboratory will be organized and equipped to effectively carry on the work for which it was established."

RULES FOR THE SUPERVISION OF THE A. PH. A. LABORATORY.

The Supervisory Committee.—The Committee on A. PH. A. Laboratory shall consist of five members elected by the Council of the ASSOCIATION to have supervisory charge of the Laboratory, one member to serve for a term of five years, one for a term of four years, one for a term of three years, one for a term of two years, one for a term of one year and after the expiration of the one-year term, one member shall be elected annually for a term of five years. The Committee shall consist of members of the A. PH. A. so chosen that at least one but not more than two members shall represent, respectively: (*a*) college of pharmacy faculties, (*b*) industrial pharmaceutical organizations, (*c*) research outside of the pharmaceutical field, and (*d*) retail pharmacy through the Council of the A. PH. A. The Chairman of the Committee shall be elected annually by the Council. The Chairman of the U. S. P. Revision Committee, the Chairman of the Committee on National Formulary, and the Chairman of the Committee on Recipe Book shall be ex-officio members of the Committee without vote.

The Advisory Committees.—For the purpose of bringing to the Laboratory the experience of the manufacturing laboratories, the Committee on Laboratory shall invite five members of the Pharmaceutical Contact Committee of the American Drug Manufacturers' Association and the American Pharmaceutical Manufacturers' Association to serve as an Advisory Committee to the Laboratory, both to advise as to the research program and to secure the coöperative study by the manufacturing laboratories of the monographs and tests proposed by the Laboratory.

Advisory Committees representing retail pharmacy and other divisions of pharmacy may be provided by the Committee on Laboratory with the approval of the Council.

Meetings of the Committee.—The Committee on Laboratory shall meet in Washington on the Monday after the first Sunday of January, April, July and October of each year unless a different time or place for any meeting shall be agreed upon by the Committee. The travel expense of the members of the Committee shall be provided for in the Laboratory budget.

The Advisory Committee of the Laboratory may be invited by the Chairman of the Laboratory Committee to meet at the same time either separately or conjointly.

Business may be brought before the Committee on Laboratory by mail and the Chairman

of the Committee may conduct such business by mail as cannot be deferred to the regular meeting of the Committee.

The Laboratory Personnel.—The Committee on Laboratory shall select the administrative head of the Laboratory and fix his compensation, subject to the approval of the Council. The tenure of the administrative head shall be for one year, and he shall not be removed during that time except after a hearing by the full Committee.

The Committee, with the advice of the administrative head of the Laboratory and the approval of the Council, shall select and fix the compensation of the other members of the Laboratory staff. Appointments of other employees than the administrative head of the Laboratory shall be for one year, but may be terminated upon two months' notice in writing because of failure of funds or of incompetence. Such notice shall be given by the Chairman of the Committee only after vote by the Committee.

The Laboratory Budget.—The Committee on Laboratory shall submit to the Council annually a budget for the Laboratory, and shall approve in advance, upon recommendation of the administrative head, all expenditures against this budget. However, the Committee may assign to the administrative head a revolving fund of fifty dollars for minor cash expenditures.

Projects for the Laboratory.—The Chairman of the N. F. Revision Committee shall submit to the Committee on Laboratory such projects as he desires to have investigated by the Laboratory, and shall likewise state their relative order of importance, and the final approval of such projects shall be by the Committee for the purpose of keeping expenditures thereon within budgetary limitations.

If grants to the Laboratory be made on behalf of the Recipe Book or the U. S. Pharmacopœia, the chairmen of the respective revision committees shall submit their projects in the same manner for the approval of the Committee.

When any project has been approved by the Committee on Laboratory, the Chairman of the Committee shall so advise the administrative head of the Laboratory, upon a suitably numbered form, and shall indicate the relative importance of the problem. The administrative head shall thereupon assign the problem to a member of the Laboratory staff who shall be responsible for the study.

Responsibilities of the Administrative Head.—The administrative head of the Laboratory shall be responsible for the actual conduct of all investigations by the Laboratory. It is expected that he will confer regularly with all members of the Laboratory staff, direct the searching of the literature, and assist in planning the program of Laboratory work.

All correspondence and all reports pertaining to the Laboratory shall be in charge of the administrative head of the Laboratory. He shall approve all letters pertaining to laboratory activities written by other members of the staff, and his decisions on such correspondence shall be final unless overruled by the Committee. In case of doubt regarding the propriety of any action he shall refer the question to the Secretary of the AMERICAN PHARMACEUTICAL ASSOCIATION for adjudication.

The administrative head of the Laboratory shall have supervision of the research projects supported by research grants made by the Council to colleges of pharmacy or other institutions. He shall confer with those directing or performing each research, and guide in the research. The person in charge of the research project at the institution to which a research grant is made shall report monthly to the administrative head of the Laboratory the detailed progress and accomplishments of the research.

Reports.—The Committee on Laboratory shall prepare the necessary rules governing the actual conduct of the Laboratory, the keeping of laboratory records and the preparation of necessary reports. Such rules and regulations, after adoption by the Committee, shall be submitted to the Council for the information of its members.

(*Motion No. 21*) It is moved by Gathercoal that the Rules for the Supervision of the Laboratory be approved as submitted, that George D. Beal, Carson P. Frailey, Charles B. Jordan, John C. Krantz, Jr., and Joseph Rosin be elected as members of the permanent Committee on Laboratory to serve five, four, three, two and one years, respectively, with George D. Beal as Chairman for the first year, from the time of the next annual meeting, and that the Chairman of the U. S. P. Revision Committee, the Chairman of the Committee on National Formulary and

the Chairman of the Committee on Recipe Book shall serve as ex-officio members of the Committee.

A vote on this motion will be called for in one week's time, in order that arrangements can be made for the meeting of the Committee, if the recommendations are approved.

54. Applicants for Membership. The following applications, properly endorsed and accompanied by the first year's dues, have been received:

No. 339, Gregory V. Senturo, 227 E. Hopkins Ave., Redwood City, Calif.; No. 340, Jun Ted Ajari, P. O. Box 17, Danville, Calif.; No. 341, Frank F. Nakamura, 208 Oak St., Marysville, Calif.; No. 342, John A. Fouch, Maxwell, Calif.; No. 343, James S. Hill, 663 Main St., Niagara Falls, N. Y.; No. 344, Francis P. Taylor, 2236 LaSalle Ave., Niagara Falls, N. Y.; No. 345, Clayton S. Heinze, 1631 Cleveland Ave., Niagara Falls, N. Y.; No. 346, Elliot G. Nablo, Sanborn, N. Y.; No. 347, Vaso Chelovich, 2759 Logan Blvd., Chicago, Ill.; No. 348, John F. Moreth, 3008 Belmont Ave., Chicago, Ill.; No. 349, Edith C. Schmitz, 203 E. Main St., Platteville, Wis.; No. 350, Edwin S. Schweger, 100 N. Broadway St., Green Bay, Wis.; No. 351, W. Alan Ries, 2720 Birch St., Alhambra, Calif.; No. 352, Abraham M. Gordon, 1815 E. 2nd St., Los Angeles, Calif.; No. 353, Cornelius F. Abbondante, 16 Vosseller Ave., Bound Brook, N. J.; No. 354, Russell H. Stimson, 1265 Cleveland Hgts. Blvd., Cleveland Hgts., Ohio; No. 355, Sister Mary Dympna Connor, Convent of Our Lady of Angels, Glen Riddle, Pa.; No. 356, Oscar Lerner, 967 Aldus St., New York, N. Y.; No. 357, David L. Kahl, 1000 J St., Sacramento, Calif.; No. 358, Selma Adams, 65 Wegman Pky., Jersey City, N. J.; No. 359, Henry C. Ruttan, 2579 Portage Ave., Winnipeg, Canada; No. 360, Dan D. Evans, San Juan Pharmacy #2, Orlando, Fla.; No. 361, James M. Casterline, Grandview Hospital, La Crosse, Wis.; No. 362, Bettie Brokaw, 1321 Colby, Everett, Wash.; No. 363, Valerie H. Ellingen, 3530 S. E. Main St., Portland, Ore.; No. 364, Elmer G. King, 7041 S. Union Ave., Chicago, Ill.; No. 365, Sidney C. James, 29 Monticello Pl., Buffalo, N. Y.; No. 366, Mearl De Ver Pritchard, 35 North St., Buffalo, N. Y.; No. 367, John H. Raven, 8 Bishop Pl., New Brunswick, N. J.; No. 368, Lloyd H. Kortum, 308 Washington Blvd., Oak Park, Ill.; No. 369, John J. Seiberz, 1266 S. Shelby St., Louisville, Ky.; No. 370, Leslie C. Jayne, 600 Lafayette Ave., Brooklyn, N. Y.; No. 371, Herbert R. Mull, 5442 N. Capitol Ave., Indianapolis, Ind.; No. 372, Guy S. Dunbar, 400 E. 58th St., New York, N. Y.; No. 373, Chester E. Watkins, 3837 N.E. Union Ave., Portland, Ore.; No. 374, A. Wray H. Hilts, 7620 Buffalo Ave., Niagara Falls, N. Y.; No. 375, Alfred E. Berkowitz, 3734 Cortland Ave., Detroit, Mich.; No. 376, Floyd J. LeBlanc, c/o State College, Brookings, S. Dak.; No. 377, Julian D. Freeman, 6246 33rd St. N.W., Washington, D. C.; No. 378, Elizabeth K. Neufield, 5230 Blackstone Ave., Chicago, Ill.; No. 379, Virginia Y. Bacon, 1507 Redondo Blvd., Los Angeles, Calif.

(*Motion No. 22*) Vote on applications for membership in the ASSOCIATION.

E. F. KELLY, *Secretary.*

COLLEGE OF PHARMACY PLANNED FOR MANCHOUKUO.

Permission has been granted by the Home Ministry of the Manchoukuo Government for the establishment of a college of pharmacy which has been planned for some years. The training institute of pharmacists now established within the Manchuria Medical University will be made the basis of the proposed college. Dr. Taizo Yamashita of the Manchuria Medical University is slated for the head of the new college, which will be built at the city of Mukden at the cost of 80,000 yen, capable of accommodating three hundred students.

EDITORIAL NOTES

CORRECTION CONCERNING KAPPA PSI.

The announcement concerning the **Kappa Psi Pharmaceutical Fraternity,** published in the April 1938, issue (page 359) of THIS JOURNAL, is incorrect. We regret the errors and are pleased to publish the following corrections:

(1) The national officers of Kappa Psi are: Dr. H. W. Youngken, of Boston, *Grand Regent;* Dean C. L. O'Connell, of Pittsburgh, *Grand First Vice-Regent;* Dr. Horatio C. Wood, Jr., of Philadelphia, Pa., *Grand Second Vice-Regent;* Dean C. E. Mollett, *Grand Third Vice-Regent;* Dr. A. Richard Bliss, Jr., *Grand Secretary and Treasurer;* Dean G. C. Schicks, of Newark, N. J., *Grand Historian;* Dr. L. Templeton, of Chicago, *Grand Ritualist;* and Dean A. O. Mickelsen, *Grand Counselor.* These officers were elected and installed at the meetings in New York City during August 1937.

(2) There will not be a convention of Kappa Psi at Minneapolis in connection with the annual meeting of the AMERICAN PHARMACEUTICAL ASSOCIATION. The usual, informal luncheon or dinner will be held during those meetings as has been customary for many years.

GEORGIA DRUG LAW—STATE'S OKAY ON NEW DRUGS ASKED IN GEORGIA.

The text of the bill follows:

Be It Enacted by the General Assembly of Georgia, and it is hereby effected by the authority of the same as follows:

DATE MUST BE SUPPLIED.

(*b*) To enable the State Chemist and the State Department of Public Health to make a finding on any such drug the packer thereof shall submit to each of these Departments (1) full reports of investigations which have been made to show whether or not each drug is safe for use; (2) a full list of the articles used as components of such drug; (3) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing and packing of such drug; (4) a full statement of the composition of such drug; (5) such samples of such drug and of the articles used in components thereof as the State Chemist and the State Department of Public Health may require; and (6) specimens of all proposed labeling for such drug.

(*c*) To aid and advise them in making such finding the State Chemist and the Director of the State Department of Public Health are hereby authorized to use such data as are available in the offices of: the Public Health Service of the United States, the American Medical Association, the United States Pharmacopœial Convention, the AMERICAN PHARMACEUTICAL ASSOCIATION, and the Food and Drug Departments of the Federal and State governments, in formulating conclusions regarding a drug or combinations of drugs.

JOINT NOTICE OF FINDING.

(*d*) If the State Chemist and the Director of the State Department of Public Health find that (1) such investigations include tests by all existing methods reasonably applicable to such drug; (2) the results of such tests do not show that each drug is unsafe for use as prescribed, recommended or suggested in the labeling thereof; (3) the methods used in, and the facilities and controls used for, the manufacture, processing and packing of such drug are adequate to preserve the identity, strength, quality and purity thereof; and (4) that such drug otherwise complies with the other provisions of the Federal or State Food and Drug Acts, they shall issue to such packer a joint notice of finding that each drug is not unsafe for use. In case either the State Chemist or the Director of the State Department of Public Health refuses to issue such notice they shall notify the packer of their reasons for such refusal.

(*e*) The State Chemist and the Director of the State Department of Public Health of the State Department of Public Health shall promulgate regulations for exempting from the operation of this Act drugs intended solely for investigational use by persons qualified by scientific training and expectance to make investigations as contemplated by this Act.

Section 2. The definition of what constitutes a new drug shall include (2) substances which have not been used sufficiently as a drug to become generally recognized as safe, (*b*) combinations of well-known drug substances where such combinations have not been generally recognized as safe, and (*c*) well-known

drug substances and drug combinations bearing labeled directions for higher dosage or more frequent dosage or for longer duration of use than has been generally recognized as safe.

Section 3. Any person who shall violate the provisions of Section 1 of the Act shall on conviction be punished as for a misdemeanor.

Section 4. The State Department of Public Health is charged with the enforcement of the provisions of this Act by and through its Director and his duly appointed agents.

Section 5. All laws and parts of laws in conflict herewith are hereby repealed.

STATE UNIVERSITY OF IOWA, COLLEGE OF PHARMACY.

Among the prizes awarded at the end of the school year are several recommendations to membership in the AMERICAN PHARMACEUTICAL ASSOCIATION and dues for one year.

Gordon H. Sheffield of Storm Lake, Iowa, a junior, was awarded membership in the ASSOCIATION for attaining the highest rank in Pharmacognosy, the prize being offered by Dean Emeritus, Wilber J. Teeters.

The Scherling prize, membership in the ASSOCIATION, given by Mrs. Gus Scherling of Sioux City in memory of her husband, a long-time pharmacist there, was awarded to Rosalie Lazriowich, St. Joseph, Mo.

Membership in the ASSOCIATION given by Professor Zada M. Cooper to the student ranking highest in Operative and Manufacturing Pharmacy was awarded to Frederick A. Quire of Kanawha, Iowa, a sophomore student.

A year's subscription to the JOURNAL OF THE ASSOCIATION given by Dean R. A. Kuever to the first-year student ranking highest in Operative Pharmacy was won by Howard L. Johnson of Chariton, Iowa.

OCCASION EXTRAORDINARY!

On the night of Saturday, June 4th, the California Pharmaceutical Association, the Northern California Retail Druggists' Association and the Southern California Retail Druggists' Association, in coöperation with local druggists' associations, together with the Alliance of Retail Trade Associations gave a dinner in honor of Edward Sidney Rogers.

In the afternoon, at the regular commencement exercises, the University of Southern California conferred the degree of Doctor of Pharmacy upon Mr. Rogers. The conferring of this degree and the dinner in his honor are in recognition of the monumental contribution he has made to the cause of Fair Trading. Mr. Rogers battled for the right of contract such as is provided for in our fair trade laws long before we had any such laws on our statute books. He is author of Section $1^1/_2$ of the Fair Trade Act and was the principal legal counsel in the Fair Trade case before the Supreme Court of the United States, who declared the Act constitutional in a unanimous decision.

Mr. Rogers has been honored by several of the presidents of the United States, as well as by his own profession.

DECENNIAL MEETING OF THE CLASS OF 1928, COLUMBIA UNIVERSITY, COLLEGE OF PHARMACY.

The University Class of 1928, Columbia University College of Pharmacy, has maintained a class organization since graduation and met at least once yearly. This, the 10th anniversary, was celebrated by a dinner on June 6th. Despite the fact that the members of the class are widely scattered over the country, twenty-one attended the reunion. The faculty was represented by Deans Ballard and Arny; and Professors: Hart, Brown, Carter, A. Taub and Dorfman.

A short meeting was held after the dinner and officers were elected. It was resolved to continue annual meetings and all members of the class are urged to notify the secretary of changes in address.

The class in successfully maintaining a connection with the College after graduation hopes that the plan will extend to other classes. It is glad to join '88 and '13 in showing that the College of Pharmacy graduates are not lacking in loyalty to their school.

THE PLANT SCIENCE SEMINAR.

The 16th annual Seminar will meet this year in the city of its birth, with Prof. Earl B. Fischer in charge. A most interesting program has been outlined and many festivities will mark the occasion, under dates of August 16th to 19th, just one week preceding the Convention of the A. PH. A.

SOCIETIES AND COLLEGES.

St. Johns University, College of Pharmacy, celebrated its Commencement Exercises on June 7th, at the Academy of Music, Brooklyn, N. Y.

Connecticut College of Pharmacy held its Commencement Exercises on June 7th, Sprague Memorial Hall, Yale University, New Haven. Dean Hugh C. Muldoon, Duquesne University, School of Pharmacy, made the address.

Hugh P. Bierne, of New Haven, was awarded the Honorary degree of Doctor of Pharmacy at these exercises. Dr. Bierne is Secretary of the Connecticut State Commission of Pharmacy, president of the Executive Committee of the National Association of Retail Druggists and a retail pharmacist.

The Board of Trustees of the Connecticut College of Pharmacy has recently elected three new members to the Board to fill vacancies. The newly elected trustees are Reverend Dr. Theodore A. Fischer, Pastor of the Church of the Messiah, New Haven; Dr. A. L. Omohundro, Director of the Laboratories of McKesson and Robbins Co., Fairfield, Conn.; and Dr. John Bolles, a practicing dentist of Danbury, Conn., a former pharmacist, and a graduate of the College of Pharmacy of the City of New York, and a member of the A. Ph. A.

Alumni Day at Philadelphia College of Pharmacy and Science was celebrated Tuesday, June 7th. On this day, especially, the College is turned over to the Alumni Association for class reunions, dinners and other festivities. On Wednesday, June 8th, the Commencement Exercises were celebrated. On this occasion three men, prominent in pharmacy, received honorary degrees.

George W. Merck, president of Merck & Co., Rahway, N. J., for his outstanding services in the fields allied to public health in the developments of newer medicinals, Doctor of Pharmacy.

Dr. Arno Viehoever, Research Chemist of the Philadelphia College of Pharmacy and Science, for his development of the outstanding new method of experimental laboratory work using transparent animals as test media, Doctor of Pharmacy.

Dr. Marvin R. Thompson, Professor of Pharmacology in the School of Pharmacy, University of Maryland, Baltimore, Md., for his pioneer work in pharmacologic researches in the field of ergot therapy, Master in Pharmacy.

In addition to these honorary degrees, ninety-two students from many parts of the United States and foreign countries, including one from British India, received degrees in Bacteriology, Biology, Chemistry and Pharmacy.

In celebration of the twenty-fifth anniversary of their graduation, the Class of 1913 of the College of Pharmacy of Columbia University, held a reunion luncheon on May 25th, at the Hotel Empire. Many of the class had not met since leaving College but the remembrances of outstanding characters were still fresh in mind after a quarter century.

In greeting the class Dean Ballard asked that the occasion be considered a new commencement and one with an experience of twenty-five years behind it and hoped that it would be a beginning in building up an association with the College which would endure for many years. President Taub of the Alumni Association spoke on the creation of a Class Fund in connection with the College Endowment.

Immediately following the luncheon a meeting of the class was called, officers were elected and Secretary Solomon Weinstein, 3680 Broadway, New York, N. Y., requested to compile records of the class and arrange for future meetings.

Commencement Exercises of the University of Maryland, School of Pharmacy, were held at College Park, June 4th, in the Ritchie Coliseum. Forty-seven students had the degree of Bachelor of Science in Pharmacy conferred upon them.

On Thursday, June 2nd, three generations of pharmacists in the **Wich** family, all graduates of the University of Maryland, attended the banquet of the Alumni Association of the School of Pharmacy, at the Lord Baltimore Hotel. They were: **Conrad L. Wich,** '82; **Henry E. Wich,** '09; and **J. Carlton Wich,** '38.

The Medical College of Virginia, Richmond, Va., celebrated its Centennial Program at St. Paul's Church, Tuesday, June 7th. The occasion was a most interesting one.

The Louisville College of Pharmacy held its Commencement Exercises on Tuesday afternoon, June 7th, at Scottish Rite Temple. Nineteen graduates received Bachelor of Science in Pharmacy degrees.

The Honorary Degree of Doctor of Laws (L.L.D.) was conferred on **Roy B. Cook,** at Charleston, W. Va., by the University of West Virginia at its Commencement held at Morgan-

town, June 7th. In the citation reference was made to his distinguished service to his state and nation in the field of History and Pharmacy. Dr. Cook is secretary of the West Virginia Board of Pharmacy, served as President of his state association, as Chairman of the House of Delegates, A. PH. A., and has held many other offices in Pharmacy.

The University of Pittsburgh, College of Pharmacy, held its Commencement Exercises at the Stadium, Wednesday, June 8th. Forty-one students had the degree of Bachelor of Science in Pharmacy conferred upon them.

The University of Illinois College of Pharmacy held its Commencement Exercises at the Civic Opera House, June 10th. Forty-five students received their diplomas, six of them being women. It is believed that from now on classes will be larger, as the present Junior class numbers more than ninety.

Brooklyn College of Pharmacy, Long Island University, held its forty-eighth Commencement this year. Dr. E. L. Newcomb addressed the graduates, who numbered seventy-four.

At the Commencement Exercises of the Kansas City College of Pharmacy, May 26th, **Dean David Whitney** received the honorary degree of Master of Science. Seventeen students received the Bachelor of Science degree at the same time, and each of them has been placed in a position. The graduates received complimentary memberships in the Missouri and Kansas Pharmaceutical Associations.

Indianapolis College of Pharmacy held its Commencement Exercises on June 8th. Diplomas were presented to forty students, by Mr. F. E. Bibbins, president of the Board of Trustees.

Cincinnati College of Pharmacy held its Commencement recently, at which time r. George D. Beal, former President of the A. PH. A., addressed the graduates, who numbered thirty-eight.

Rutgers University, New Jersey College of Pharmacy, held its Commencement on June 8th, at which time **Harry J. Schnell,** editor of the *Oil, Paint and Drug Reporter, Druggists Circular* and *National Painters' Magazine,* received the Honorary Degree of Doctor of Pharmacy.

PERSONAL AND NEWS ITEMS.

A testimonial dinner in honor of **Dr. Ivor Griffith** was tendered at the Manufacturers and Bankers Club, Philadelphia, June 7th. The speakers were: Dr. Wilmer Krusen, President of the College; Hon. Arthur H. James, Judge of the Superior Court of Pennsylvania; Dr. C. C. Williams, President, Lehigh University; Colonel Samuel Price Wetherill, Chairman, Board of Trustees; Dr. E. Fullerton Cook, Professor of Operative Pharmacy and Chairman, Revision Committee, U. S. P.; Hon. Theodore Rosen, Judge, Court of Common Pleas of Philadelphia; Dr. J. W. Sturmer, Dean of Science.

The Delaware Pharmaceutical Association Convention was held at Hotel Henlopen, Rehoboth, June 29th and 30th. An interesting program was arranged and many festivities were enjoyed.

Since the dedication of the new home of Mellon Institute, the building has become the center of scientific meetings in Pittsburgh. The accomplishments of the research staff during the past year have proved the value of the new facilities. New enthusiasm, and a greater desire on the part of the Fellows to be successful in their work, is evidenced.

The Delta Sigma Theta Fraternity, Delta Chapter, Columbia University College of Pharmacy, elected **Dr. J. Leon Lascoff** and **Prof. Horace M. Carter** honorary members, at a meeting held last month. Dr. Lascoff and Professor Carter were inducted into the fraternity at a dinner given in their honor, held at the Hotel Victoria, in New York City.

Dr. Lascoff is well known to pharmacists throughout the country, is President-Elect of the AMERICAN PHARMACEUTICAL ASSOCIATION, recipient of the Remington Medal, etc. Professor Carter is very popular with the pharmacists here in the East, having taught many of them at Columbia University College of Pharmacy.

One hundred and fifty distinguished pharmacists welcomed Dr. Lascoff and Professor Carter at the dinner. Hoffmann-LaRoche, Inc., Eli Lilly and E. R. Squibb were represented.

The **Delta Sigma Theta Fraternity** is the most prominent of the Inter-Professional Fraternities, composed of physicians, dentists and pharmacists, all working together for a common cause.

The District of Columbia Pharmaceutical Association held its final meeting of the year at Wardman Park Hotel, Tuesday, June 14th, at 8:00 o'clock. The new Federal Foods, Drugs and Cosmetics Bill, Fair Trade Legislation and the D. of C. Narcotic Act, were discussed.

The Pennsylvania Pharmaceutical Association met in Wilkes-Barre, June 13th–16th. Features of the convention were "Fair Trade Clinic" and "Merchandising by Addition." Open forums, technical discussions and nationally known speakers added to the occasion, which was a very delightful one.

Utah Pharmaceutical Association met in Ogden, May 23rd to 25th. Many outstanding speakers were secured, and altogether this was one of the greatest conventions ever staged in Utah.

The New York Pharmaceutical Association held its convention at The Sagamore Hotel, Lake George, N. Y., June 19th to 22nd. John S. Norton, Vice-President of the Lambert Pharmacal Co., and Charles Luckman, Vice-President of Pepsodent Sales, Inc., were guest speakers at the Tuesday afternoon session which was devoted entirely to the subject of Fair Trade.

The 68th annual convention of the New Jersey Pharmaceutical Association was held at the Ritz-Carlton Hotel, Atlantic City, N. J., June 21st–24th. Among the speakers were: Dr. H. Evert Kendig, Dr. Ernest Little, Dean Charles Ballard, Dr. C. Leonard O'Connell, Dr. Ivor Griffith, Dr. Wm. J. Carrington and Messrs. Jerry McQuade, Charles Luckman Walter J. Quinlan and J. W. Snowden.

The Kansas Pharmaceutical Association had a splendid Pharmacy Booth with demonstrations of the preparations of galenicals and the filling of prescriptions, in the Hall of Health at Wichita, under the sponsorship of the Sedwich County Medical Society. Miss Esther H. Barney, who had charge of the A. PH. A. exhibits at Chicago and Dallas, and who has made a reputation in this work, was in charge of the Booth and spoke several times during the week, about the exhibit and Pharmacy's place in public health. It is encouraging to note the increased number of such exhibits at medical and public health exhibitions.

One of the best meetings the Wyoming Pharmaceutical Association has ever had was held in Buffalo, Wyoming, May 16th and 17th. The meetings were well attended and the members took active part in them. They were all enthusiastic and anxious to attend each session.

The monthly meeting of the Pittsburgh Graduate Chapter of Kappa Psi Pharmaceutical Fraternity was held at the Highland Country Club on May 19th. A golf tournament was held in the afternoon; initiation and a banquet in the evening, with entertainment.

F. J. STEELE, *Historian.*

REWARD FOR HERO OF YELLOW FEVER FIGHT.

John R. Kissinger, of Huntington, Ind., a hero of the yellow fever experiments in Cuba, thirty-eight years ago, and a recipient of the Congressional Medal of Honor, would receive a more material reward from his Government under terms of a bill which Representative Glenn Griswold, of Indiana, introduced. Mr. Griswold's bill would promote Mr. Kissinger to the rank of Major, with corresponding retirement pay.

Broken and in ill health, as a result of the yellow fever experiments, Mr. Kissinger left the Army in 1901 as a private. At first he received $12.00 a month, then this was increased to $125.00.

Major Walter Reed went to Cuba in 1899 to conduct experiments for determining the cause of yellow fever. Being convinced that the fever was caused by a mosquito, Major Reed decided to prove this through experiments on humans. At this time the disease was considered fatal in a large percentage of cases. Mr. Kissinger was the first to volunteer to contract the disease. His nerves were badly shattered and he was paralyzed from the hips down for about ten years.

Mr. Kissinger's comment is, "I was glad to get a chance to save lives instead of ending them, which is usually considered the work of an Army man during war."—*Washington Star* (June 13, 1938).

The British Pharmaceutical Conference will hold its seventy-fifth annual meeting in Edinburgh, September 12 to 16, 1938.